PLASMA AMINO ACID LEVELS IN OBESITY:
EFFECTS OF INSULIN RESISTANCE

Benjamin Caballero, Nicholas Finer
and Richard J. Wurtman

Department of Applied Biological Sciences and
Clinical Research Center
Massachusetts Institute of Technology
Cambridge, MA 02142

ABSTRACT The decreased insulin sensitivity of obesity, besides its well-known effects on glucose metabolism, is also responsible for the elevated plasma amino acid levels observed in many obese persons. This hyperaminoacidemia is most evident for valine, leucine, isoleucine, tyrosine and phenylalanine. The plasma amino acid response to food intake is also different in obese subjects; carbohydrate meals do not cause the expected fall in branched chain amino acids, causing a distorted postprandial amino acid profile.

INTRODUCTION

Most moderately obese persons have a normal oral glucose tolerance test (OGTT), but they exhibit an excessive insulin rise in response to glucose intake, consistent with their lower tissue responsiveness to insulin. This hyperinsulinemia of obesity was first described over 20 years ago (1), and is associated with a decreased glucose metabolic rate, excessive hepatic basal glucose production, and inadequate suppression of hepatic glucose output by insulin (2). Obese persons may thus be chronically exposed to high plasma insulin concentrations, which may be necessary to sustain their normal blood glucose levels, but which may be

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1. Present address: Department of Medicine, Guy's Hospital Medical School, University of London, London, England
either insufficient, or excessive for other insulin-dependent processes.

The decreased tissue sensitivity to insulin of obesity involves receptor and postreceptor defects. Studies in obese humans and in animal models of obesity have shown a decreased number of insulin receptors in a variety of tissues: skeletal muscle (3, 4), adipocytes (5), thymic lymphocytes (6), hepatocytes (7, 8) and circulating monocytes (9). Studies in humans have also demonstrated a correlation between the number of receptors in circulating monocytes and insulin sensitivity measured by the insulin clamp technique (10). Regional perfusion studies in obese humans show that insulin resistance is present in muscle (quantitatively the most important) (11), adipose tissue, liver (2) and the splanchnic bed (12, 13). Since under normal conditions only a small number of receptors must be active to exert insulin actions, most obese subjects exhibit a normal maximal insulin stimulated glucose disposal rate when sufficient insulin is administered (14). On the other hand, some obese persons cannot reach the maximum glucose output even when receiving very high amounts of insulin, presumably reaching receptor saturation without exhibiting an insulin effect (15, 16). These obese persons are characterized as having postreceptor defects, and in some studies the magnitude of this defect is correlated with fasting plasma insulin concentrations (16).

INSULIN AND PLASMA AMINO ACID LEVELS IN OBESITY

Normal insulin effects on plasma amino acids

Insulin regulates protein synthesis at the transcriptional, translational and post-translational processing steps (17, 18); it can also indirectly modulate protein synthesis by controlling the rate of amino acid uptake into the cell. Insulin promotes the incorporation of branched chain amino acids into muscle, inhibits leucine oxidation (19), and decreases protein degradation (20). In 1928, Luck et al. (21) were the first to demonstrate that the injection of insulin to man produces a significant decrease in total amino N in plasma. In the following decades, an inverse correlation between plasma insulin and branched chain amino acid concentrations over a wide range of insulin levels have been reported, from very low, such as in diabetes, to very high, as in functioning insulinoma (22). A dose of 0.1 U/kg of insulin in an adult causes a significant fall in branched chain amino acids 20 minutes after injection (23); carbohydrate intake produces similar
effects (24). This insulin effect is most likely due to a stimulation of peripheral amino acid uptake, particularly into muscle tissue (25). In a recent study, Fukagawa et al. (26) used the euglycemic clamp technique to quantify the sensitivity of the branched chain amino acids, tyrosine and phenylalanine to insulin in normal men. They reported that insulin levels for half-maximal amino acid decrease are within the range of half-maximal glucose disposal.

Insulin and plasma amino acids in obesity

Several years ago, Felig et al. and others (27, 28) demonstrated that the insulin-dependent fall in plasma BCAA was impaired in obese subjects; in their study, obese subjects showed significantly higher fasting plasma levels of valine, leucine, isoleucine, tyrosine and phenylalanine. After i.v. administration of 0.5 g/kg of glucose, the percent fall in neutral amino acids was significantly lower in obese, although the absolute fall for each of these amino acids was similar in lean and obese. Felig et al. suggested that this hyperaminoacidemia could constitute a feedback signal to increase insulin production in face of the lower insulin sensitivity, given the known ability of most amino acids to stimulate pancreatic beta cell output (29). An alternative interpretation is that this elevated plasma amino acid levels result from the accumulation of amino acids within the plasma compartment, secondary to a decrease in their insulin-mediated uptake into peripheral tissues. This interpretation assumes that insulin resistance affects similarly glucose and amino acid metabolism. Although in normal humans the plasma insulin level for half-maximal glucose metabolic rate and half-maximal decrease in plasma amino acid levels is similar (26), it is not known if this is the case in insulin-resistant states. Indeed, it has been shown that there is a dissociation between the responsiveness to insulin of glucose and of potassium and free fatty acids (30). Insight in the mechanism of insulin resistance obtained from the study of other diseases also suggest that the responsiveness of glucose and amino acid uptake to insulin may not necessarily be parallel (Table 1). For example, the insulin resistance of uremia is associated with a decreased metabolic rate for glucose, but amino acid uptake is normal, to the point that the high plasma insulin response frequently produce a markedly low plasma level of branched chain amino acids (31, 32).
Likewise, aging is associated with a progressive decline in the glucose metabolic response to insulin, while the amino acid response is preserved (33). In obesity, results from other studies show that the hyperaminoacidemia is not a constant feature of insulin resistance (34, 35). In contrast to Felig et al., studies by Forlani et al. (34) and Heraief et al. (35) found normal fasting plasma levels of branched chain amino acids in obese, which were unrelated to plasma insulin concentrations. A study that compared the rate of disappearance from plasma of an I.V. valine dose in lean and obese adults, found that the metabolic clearance rate of the amino acid was the same in both groups, and that the obese actually had lower valine levels during the first 90 minutes of the study (36). Conversely, Forlani et al. (34) found a reduced fall in plasma branched chain amino acid in the obese during an euglycemic insulin clamp. These investigators used a nonprimed insulin infusion and assumed a steady-state condition after only 30 minutes, factors that may have complicated the interpretation of results.

If the degree of hyperinsulinemia of an obese person is insufficient to support a normal amino acid metabolism, this person would be in a situation of relative insulin deficiency (as far as amino acids are concerned), similar to that of an insulin-
deprived type I diabetic. In this latter condition, there is an increase in the plasma concentration of BCAA, as well as in the rate of leucine flux and oxidation (37). Kinetic studies in obesity using stable isotopes also suggest that leucine flux may be above control levels. Vazquez et al. (38) studied a group of obese persons using a primed, 3-hour $^{14}$C-leucine infusion, and reported a mean leucine flux ($Q$) of 8.7 mmol/hour. A similar result (8.44 mmol/hour) was found by Chugston et al. (39) in 10 obese women infused with $^{14}$C-leucine for 24 hours. Using a constant 10-hour infusion of the same tracer, Garlick et al. (40) found a mean $Q$ of 10.2 mmol/hour (97.3 umoles/kg/hour) in five obese adults. These values are higher than those found by Fukagawa et al. (20) in five lean adults using $^{13}$C-leucine and a similar kinetic model: 5.7 mmol/hour (76.8 umoles/kg/hour). However, comparisons between different studies should be made with caution, since differences in methods and/or theoretical assumptions in the kinetic parameters may produce differences unrelated to the physiological state of the subjects. Ideally, data from obese subjects should be compared only with a carefully matched group of lean subjects studied under the same conditions. Furthermore, as with other values of substrate concentrations in obese, results can vary dramatically depending on whether they are expressed per kg of body weight, or lean body mass or surface area, and most studies on amino acid kinetics do not assess body composition.

Effects of body composition on plasma amino acids

The correlation between fat mass and insulin sensitivity has been shown in several studies. Bjorntorp et al. (41) found a significant correlation between fasting insulin levels and fat cell diameter in obese persons, and the correlation of fasting insulin with body fat and with percent excess of IBW has also been reported by other investigators (42, 43). Measuring insulin sensitivity with the euglycemic clamp technique, Yki-Jarvinen and Koivisto (44) reported a significant negative correlation between percent body fat (estimated by skinfold thickness measurements) and insulin sensitivity. Bogardus et al. (45) also reported a nonlinear correlation between insulin sensitivity and fat mass measured by underwater weighing, with a cut-off point at approximately 28% of body fat. Using the steady state plasma glucose approach, Nagulesparan et al. (46) found a significant
negative correlation between body mass index and insulin response.

Plasma amino acid levels in obesity also appear to be affected by body composition. Lean tissue is the main site of metabolism of branched chain amino acids, and obesity is usually associated with an increase in lean body mass that may comprise as much as 40% of the excess weight (48). One study showed a significant correlation between plasma amino acids and insulin levels and ponderal index of obesity (49). In another study in obese subjects before and after a 6-week period of physical training, a significant positive correlation was found between lean body mass (measured by 40K) and the sum of branched chain amino acids, tyrosine and phenylalanine, both before and after the training (47) (Figure 1).
Plasma amino acid levels and brain serotonin in obesity

High plasma levels of large neutral amino acids (LNAA) -of which the branched chain comprise a large fraction- may affect the regulation of food intake and other behavioral and neuroendocrine processes involving the neurotransmitter serotonin. The synthesis of serotonin in the brain is dependent on the availability of its precursor amino acid tryptophan, which enters the brain at a rate determined by its plasma concentration relative to the other large neutral amino acids (LNAA: valine, leucine, isoleucine, tyrosine, phenylalanine and methionine) (50). This plasma Trp/LNAA ratio, therefore, predicts the availability of tryptophan to the brain (51), which in turn determines its serotonin output in animals, and presumably in humans (52, 53).

TABLE 2
CARBOHYDRATE-INDUCED FALL IN PLASMA NEUTRAL AMINO ACIDS IN OBESE
Mean % decrease from basal levels

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<thead>
<tr>
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<th>Lean</th>
<th>Obese</th>
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<tbody>
<tr>
<td>Val</td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td>Ile</td>
<td>57</td>
<td>31</td>
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<tr>
<td>Leu</td>
<td>53</td>
<td>25</td>
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<td>Phe</td>
<td>45</td>
<td>22</td>
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<tr>
<td>Tyr</td>
<td>52</td>
<td>24</td>
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<tr>
<td>Trp</td>
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The insulin resistance of obese persons diminish the insulin-mediated fall in plasma LNAA and therefore blocks the normal rise in the Trp/LNAA ratio produced by carbohydrate ingestion. Thus, less tryptophan would be available to the brain, and less serotonin will be released after a carbohydrate meal. Since serotonin agonists have been shown to selectively decrease carbohydrate intake in obese "carbohydrate cravers" (54), and tryptophan administration decreases appetite and energy intake in normal humans (55, 56), the "carbohydrate craving" described in some obese persons (54) may be teleologically interpreted as the failure of the brain to produce enough serotonin to suppress
carbohydrate intake. To assess the magnitude of this impaired Trp/LNAA "signal" to the brain in obese subjects, we compared the plasma amino acid profile in lean and obese after ingestion of carbohydrate snacks at mid-afternoon. Seven obese persons (57% of ideal body weight between 135 and 190) and six lean controls received a standard breakfast at 7:30 AM, and a 400 kcal lunch (15% protein, 55% carbohydrate and 30% fat) at noon. Two hours later they received a 30g glucose drink. Plasma amino acids, glucose and insulin were measured at hourly intervals until 6 PM. The plasma glucose response in the obese was similar to controls, but the obese showed a significantly higher insulin response (peak level, mean ± SD: 73 ± 37 μU/mL, vs. 13 ± 4 μU/mL in controls). In spite of this higher insulin output, the fall in plasma neutral amino acids was markedly blunted (Table 2). As a consequence of this blunted amino acid response, obese subjects exhibited only a 6% rise in their Trp/LNAA ratio in response to carbohydrate ingestion, reaching a peak ratio of 0.107 ± 0.013, as compared to 0.150 in lean controls.

CONCLUSIONS

Most obese persons show elevated plasma insulin levels, in order to compensate for the very frequent insulin resistance associated with obesity. This hyperinsulinemia is usually sufficient to sustain a normal plasma glucose concentration, but this is not the case for plasma amino acids, which are usually elevated, particularly the branched chain, tyrosine and phenylalanine. In contrast, plasma tryptophan tend to be below control levels. The net result is a decreased ratio of Trp to the other neutral amino acids in plasma, and thus a lower availability of Trp to the brain. Thus, the degree of insulin resistance of an obese person, besides its effects on glucose metabolism, may also affect serotonin-mediated brain functions by limiting the supply of the precursor amino acid to the central nervous system. These data suggest that treatments that improve the amino acid response to insulin of obese persons, or that provide tryptophan supplements may be useful coadjuvants in the dietary treatment of obesity.
REFERENCES


