Regulation of Splanchnic Protein Synthesis by Enteral Feeding

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In the adult organism, maintenance of body protein stores is accomplished through a diurnal rhythm of catabolic and anabolic phases [1]. Under physiological conditions, a net loss of body proteins occurs in the interprandial periods, particularly during the night, as well as during exercise [2]. Conversely, a net protein accumulation takes place during meal absorption [3] and in the recovery phase after exercise [4]. As both protein accretion and loss are the net result of changes in protein degradation and synthesis, each of these two processes plays a key role in the maintenance of protein homeostasis.

As with those occurring at the whole body or muscle level, coordinate changes in protein synthesis and degradation are also likely to occur within the splanchnic bed during the day. However, data on in vivo splanchnic tissue protein synthesis and degradation in humans are sparse compared with those available at either the whole body or muscle level. This is because methods for studying splanchnic protein synthesis in humans are technically difficult and in some instances more invasive than those available in the whole body or in skeletal muscle. Nevertheless, there is now a considerable amount of data on the regulation of protein turnover in the splanchnic area, considered either as a whole or in individual splanchnic tissues.

Splanchnic organs are peculiar with regard to their blood circulation and the source of amino acids for their metabolic needs. The liver is a collector of blood from all the other splanchnic organs, because it is placed in series with respect to them, whereas it is placed in parallel to the systemic circulation. The gut takes up amino acids not only from the systemic circulation but also from the luminal space. Luminal amino acids in turn can derive from either mucosal cell turnover or dietary proteins.
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The components of the exchange of nitrogen compounds within the splanchnic area include: (i) net amino acid exchange; (ii) amino acid catabolism, interconversion, and biotransformation; (iii) secretion of proteins into plasma; (iv) uptake and catabolism of plasma proteins, including hormones, and (v) turnover (synthesis and degradation) of structural tissue proteins. As marked differences occur in splanchnic metabolism between the postabsorptive (that is, the fasting) state and during meal ingestion, these features would need to be studied in both periods of the day.

The study of protein metabolism in the liver, the gut, and other splanchnic organs in vivo theoretically requires the separate catheterization of the vessels which supply and drain these organs, combined with blood flow measurements, tracer amino acid infusion, and tissue biopsies, or combinations of these. In addition, the fractional synthetic rate (FSR) of either liver- or gut-secreted proteins may be measured. Obviously, some of these procedures are not feasible in the human for ethical and technical reasons. In humans, only catheterization of the splanchnic area as a whole can safely be accomplished through sampling of arterial and hepatic venous blood. By this approach, however, the splanchnic bed is considered as a single compartment – that is, the liver and the nonhepatic splanchnic organs are lumped together. While this approach represents an oversimplification, it has nevertheless provided some useful data on protein turnover in the splanchnic bed as a whole. On the other hand, catheterization of the portal, hepatic, and other splanchnic veins is applicable to experimental animal preparations.

Another approach to the study of overall splanchnic handling of dietary amino acids, without the need for catheterization, is through the combined use of oral and intravenous amino acid tracer infusions (see below). In this case as well the splanchnic area is considered as a whole.

**Fasting State**

Using the arteriovenous balance technique, it has repeatedly been shown that the splanchnic area as a whole takes up virtually all the arterial amino acids in the postabsorptive state in humans [5, 6]; therefore it is in a net, positive amino acid balance. This behavior is opposite to that observed across peripheral tissues, such as skeletal muscle, where a release of most amino acids takes place [5, 6]. Splanchnic amino acid uptake is highest for alanine, glutamine, and lysine, whereas it is low for the branched chain amino acids (BCAA) [5, 6]. As the portal vein cannot easily be sampled in humans, virtually no data are available on the separate role of the gut and the liver in the human. However, on the basis of animal studies it has been found that the gut releases the BCAA, alanine, and glycine, whereas the net balance of the other amino acids is close to zero [7–9]. The liver in turn takes up alanine, glycine, serine, and the aromatic amino acids (AAA), phenylalanine and tyrosine [7–9]. Thus tissues with functions that
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Table 1. First-pass splanchnic uptake (expressed as percent of the oral load) of selected amino acids in fasted and fed states [11–17]

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Fasting state</th>
<th>Fed state</th>
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<tbody>
<tr>
<td>Alanine, %</td>
<td>70</td>
<td>–</td>
</tr>
<tr>
<td>Arginine, %</td>
<td>39–50</td>
<td>31–44</td>
</tr>
<tr>
<td>Glutamate, %</td>
<td>≈88</td>
<td>–</td>
</tr>
<tr>
<td>Glutamine, %</td>
<td>≈54</td>
<td>–</td>
</tr>
<tr>
<td>Leucine, %</td>
<td>≈19</td>
<td>24–28</td>
</tr>
<tr>
<td>Lysine, %</td>
<td>–</td>
<td>≈30</td>
</tr>
<tr>
<td>Phenylalanine, %</td>
<td>≈33</td>
<td>45–60</td>
</tr>
<tr>
<td>Tyrosine, %</td>
<td>≈35</td>
<td>≈37</td>
</tr>
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are not essential for short-term survival provide amino acids to sustain protein synthesis within more essential organs, such as those in the splanchnic area (mostly the liver) or the kidney [6], in the interprandial periods.

Studies using the combination of isotopic and arteriovenous amino acid difference measurements have shown that – at least with regard to leucine, phenylalanine, and tyrosine – net splanchnic extraction results from simultaneous uptake and release, the former exceeding the latter [6, 10]. It is likely that simultaneous uptake and release also occurs for other amino acids. Moreover, fractional extraction of some amino acids, such as the AAA, exceeds that of the BCAA. Thus the splanchnic area shows selectivity in the uptake of circulating amino acids, and this may be related to the metabolic capacity of splanchnic (mostly liver) tissues to catabolize particularly amino acids.

Using a combination of intravenous and oral amino acid administration [11–17], the first-pass splanchnic uptake of a number of amino acids has been calculated (Table 1) [18]. Glutamate and glutamine exhibited the highest uptake, whereas the uptake of leucine was lowest. It was estimated that most of the leucine taken up was oxidized [12].

A quantitative assessment of splanchnic total protein turnover (that is, synthesis and degradation) has recently been provided in the postabsorptive human [6, 10]. Data on protein kinetics within an organ can be derived from those of essential amino acids. Thus organ protein synthesis is calculated from the rate of amino acid organ disposal minus irreversible catabolism. Conversely, its release from organ protein degradation indicates proteolysis. By knowing the (average) amino acid abundance in organ proteins, regional protein synthesis and degradation can then be estimated. Data on the splanchnic kinetics of two essential amino acids, leucine and phenylalanine, in postabsorptive humans are reported in Table 2. As regards leucine, the balance is neutral – that is, protein degradation and synthesis proceed at the same rate. This is because splanchnic leucine catabolism (that is, oxidation) is offset by a net positive amino acid uptake. However, as regards phenylalanine, protein synthesis is significantly greater than degradation, consistent with a net positive phenylalanine-derived protein balance within the splanchnic area, which has also been observed by
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Table 2. Splanchnic leucine and phenylalanine rates of release from protein degradation and disposal protein into synthesis in post-absorptive humans

<table>
<thead>
<tr>
<th></th>
<th>Degradation</th>
<th>Synthesis</th>
</tr>
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<tbody>
<tr>
<td>Leucine</td>
<td>33.6 ± 7.8</td>
<td>35.6 ± 8.1</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>10.2 ± 3.2</td>
<td>14.8 ± 2.5*</td>
</tr>
</tbody>
</table>

Data from Tessari et al. [6] and unpublished data from Tessari and Garibotto. The data are expressed as µmol/min per 1.73 m² of body surface, and were calculated using noncompartmental A–V models.

*p < 0.05 vs. degradation.

others [10]. The reason for these inconsistencies is unclear. They may reflect the type of isotope infused, the models used in the calculation, or an incomplete measurement of all amino acid catabolic pathways. In any case, it is important to recognize that, since in muscle the net protein balance is negative [6–10], peripheral tissues provide protein precursor (that is, amino acids) to visceral organs to sustain protein synthesis in the interprandial phases.

From the data of Table 2, it can also be seen that the kinetics of leucine relative to those of phenylalanine are closely proportional to the relative abundance of the two amino acids in average splanchnic proteins (that is, 9–10% for leucine; about 4% for phenylalanine). The contributions of splanchnic protein degradation and synthesis to whole body rates are about 22 and 27%, respectively [6]. These fractions are only ~30% lower (37 and 34%, respectively) than those calculated in total skeletal muscle, despite the much larger protein mass contained in the latter. Thus by assuming that the total amount of protein in the splanchnic organs (the upper gastrointestinal tract, gut, liver, spleen, and pancreas) is around 0.7–1 kg in a healthy adult human subject [6], the average fractional turnover of splanchnic proteins can be estimated to be between 12 and 15%/day. These figures are several-fold greater than those estimated in skeletal muscle proteins (1–2%/day). These different kinetic features probably allow fast-turnover proteins in the splanchnic bed to be more responsive to acute stimuli or inhibition, and therefore more acutely regulated.

Total splanchnic protein synthesis, as measured by the catheterization technique, includes synthesis of both structural and secretory proteins, such as albumin, fibrinogen, VLDL-Apo B 100, and so on. Albumin is by far the most abundant liver-secreted protein. Using isotopic amino acid infusions and precursor–product relations, it has been estimated that albumin synthesis (intra-vascular pool) is about 10–12 g/day [19, 20], and it may account for ~4–5% of whole body protein and for ~20% of splanchnic protein synthesis in the postabsorptive state. However, if one considers that only ~40% of the total albumin pool is intravascular [20], total albumin synthesis in the postabsorptive state may be up to 25–30 g/day, or between 10 and 15% of whole body protein
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Table 3. Fractional synthetic rates (FSR, expressed as percent per hour) of tissue proteins within the splanchnic area in humans

<table>
<thead>
<tr>
<th>Tissue</th>
<th>FSR</th>
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<tbody>
<tr>
<td>Esophagus</td>
<td>≈1.3</td>
</tr>
<tr>
<td>Stomach</td>
<td>≈1.8</td>
</tr>
<tr>
<td>Small intestine</td>
<td>≈2–2.5</td>
</tr>
<tr>
<td>Colon mucosa</td>
<td>≈0.4</td>
</tr>
<tr>
<td>Liver</td>
<td>≈0.9</td>
</tr>
<tr>
<td>Albumin</td>
<td>≈0.3–0.5</td>
</tr>
</tbody>
</table>

Data from references 22–26.

synthesis (which has been estimated to be about 250 g/day) [21], and 40–50% of splanchnic protein synthesis [6].

The fractional synthetic rate of a number of structural proteins in individual splanchnic tissues has also been calculated in humans by measuring the rate of amino acid tracer incorporation into the tissue by means of biopsy (Table 3). Estimates in the esophagus [22], the stomach [22], the small intestine [23, 24], the colon [25], and the liver [25] have been obtained. It can be seen that the FSR values of splanchnic proteins vary greatly. On the whole, they are several-fold greater than those of muscle proteins, particularly those of the stomach and the small intestine. In this regard, one important technical issue is that of the precursor pool employed in the calculation of FSR. This issue is particularly important for the gut mucosa, which utilizes both arterial and luminal amino acids for protein synthesis. Ideally, such a precursor is the intracellular aminoacyl-t RNA – that is, the immediate precursor of protein synthesis. Because isolation and measurement of isotope incorporation into the intracellular aminoacyl t-RNA is technically difficult, either the enrichment (or the specific activity) in the free intracellular amino acid or some surrogates in plasma have been employed. In pigs [26], the enrichment/specific activity in the leucyl t-RNA of the stomach mucosa has been reported to be indistinguishable from that of α-ketoisocaprate following 13C-leucine infusion in the postabsorptive state, and higher than that of intracellular free leucine. Therefore FSR values calculated from the free intracellular amino acid enrichments may be overestimated. This indicates also that mucosal protein synthesis may derive amino acids not only from the intracellular free amino acid pool but from plasma as well as from the gut lumen. In other words, neither the basolateral nor the apical routes are favored. However, while these findings may hold for the fasted state, they may be different in tissues from fed animals. On the other hand, intracellular free amino acids may also derive from tissue proteolysis. Indeed, the plasma enrichment of a leucine tracer given orally is greater than that achieved by an intravenous infusion, suggesting a dilution of the oral tracer by splanchnic proteolysis [11–17].
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A challenging issue is the comparison of results of splanchnic protein synthesis obtained by different methods. If one attempts to estimate total protein synthesis in splanchnic tissues from the sum of biopsy-determined FSR values, the protein content and mass of the various splanchnic tissues are required. These data are difficult to obtain, and, to my knowledge, not yet available. However, rough estimates can be derived from anatomical measures. Thus, the estimated gross total splanchnic protein synthesis (>130 g/day) would be greater than that derived from splanchnic catheterization and isotope infusion studies (about 70 g/day) [6, 10]. The reason for these apparent discrepancies is unclear. They might reflect the uncertainties mentioned above, the differences in the techniques involved in measuring protein turnover in individual tissues between direct isotope incorporation methods vs. total splanchnic estimates (by continuous infusion tracer techniques with the A-V measurements) [18], modeling problems, etc. More comparative studies are required to solve these inconsistencies.

Effects of Oral Feeding

No study is yet available on the effect of feeding on total splanchnic protein synthesis in humans. There are only a few studies on the effects on net splanchnic amino acid balance following feeding, on the synthesis of selected liver synthesized proteins, or on gut protein synthesis. It has been known for years that following a protein meal the splanchnic bed extracts alanine, glutamine, and the AAA, whereas it releases many other amino acids [5]. The BCAA represent more than one half of the total net amino acid release following a protein meal, indicating a limited uptake of these amino acids by splanchnic tissues. These findings have recently been confirmed using a physiologic common mixed meal [27]. Since about 38 and 29% of the ingested BCAA and non-BCAA, respectively, reach the systemic circulation [27], these findings also revealed an important degree of sequestration or uptake of the ingested amino acids by splanchnic organs.

More information on the relative role of the gut and liver in postprandial amino acid metabolism has been gained from animal studies [7–9]. The liver removes most of the amino acids taken up by the splanchnic area postprandially, with dominance of the gluconeogenic amino acids [7]. A complex study involving catheterization of an artery and the portal and the hepatic veins during constant leucine tracer infusion in mongrel dogs has yielded relevant information on the effects of feeding on gut and liver protein kinetics [28, 29]. Intragastric feeding increased both liver (by 6-fold) and gut (4-fold) protein synthesis (Fig. 1). This stimulatory effect was more marked using oral than intravenous feeding (Fig. 1). Thus the route of nutrient ingestion also affects the extent of the anabolic response of individual splanchnic organs to feeding.
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The quality of the ingested proteins may condition the extent of gut amino acid release (and, conversely, of gut amino acid utilization), as well as of urea synthesis. In pigs, these parameters were higher following a soy-based than a casein-based protein meal [30], suggesting a reduced use of the ingested amino acids for gut protein synthesis with soy administration. Furthermore, following ingestion of blood (which is selectively lacking in isoleucine) a greater net release of amino acids from the gut was observed than occurs with a balanced protein meal. Isoleucine replacement by an intravenous infusion reduced this excessive gut amino acid release. Thus a high protein quality favors gut protein synthesis and this may buffer the postprandial increase of amino acids in both the portal and the systemic circulation following a physiologic meal. These findings are important to understand the mechanisms of hyperammonemia in patients with liver disease following upper gastrointestinal tract bleeding. Carbohydrate ingestion also apparently enhances postprandial gut protein synthesis, as indirectly suggested by increased gut amino acid retention [30]. This indicates a role for carbohydrates in promoting protein deposition postprandially in visceral organs.

Using simultaneous infusion of oral and intravenous amino acid tracers in humans, marked differences in splanchnic amino acid uptake following feeding have been observed (Table 1) [11–17]. These differences between certain amino acids, such as leucine and phenylalanine, that are already observed in the fasting

Fig. 1. Liver and gut rates of leucine release from protein degradation, disposal into synthesis, and net balance (expressed as leucine equivalents) in dogs in the basal state and following enteral (EN) or parenteral nutrition (PN). (Compiled from references 28 and 29).

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...state were amplified by feeding. Again, as the AAA are catabolized mainly by the liver (aside from the kidneys), these differences may relate to the site of amino acid catabolism in vivo. However, as outlined above, these studies did not allow direct measurement of splanchnic protein synthesis postprandially. We recently estimated that after a mixed meal only 10% of the ingested leucine is deaminated into \(\alpha\)-ketoisocaproate at first pass [31], in agreement with the low activity of BCAA aminotransferase in splanchnic organs. Therefore, the majority of the dietary leucine taken up postprandially should have been used for splanchnic protein synthesis, in keeping with estimates in the postabsorptive state [12].

In fractional terms, first-pass splanchnic dietary leucine uptake decreased with the increase in dietary leucine load [14], suggesting decreased efficiency of splanchnic removal and resulting in more dietary leucine reaching the systemic circulation. A close correlation was also found between dietary leucine rate of appearance (Ra) and leucine concentrations postprandially, suggesting that the former is a major determinant of systemic leucine levels after a meal [14].

In humans, ingestion of a mixed meal results in a stimulation of whole body protein synthesis [3] (Fig. 2). This occurs provided that a sufficient amino acid (and/or energy) load is given – that is, between 0.1 and 0.2 g protein/kg body weight·h, at an energy intake ranging between 2.5 and 3.8 kcal/kg·h [3, 32]. We have observed a stimulation of the non-oxidative leucine disposal (NOLD) by \(\sim 10\%\), using continuous administration of a mixed meal of 15 kcal/kg body weight (containing 22% of energy as protein) over 4 h (Fig. 2) [3].

Dietary proteins are important for the postprandial stimulation of whole body protein synthesis. Indeed, when isoenergetic meals with or without amino acids were given, no stimulation of NOLD was observed with the amino acid-free meal, in contrast to what was observed with a complete meal [32, 33]. Another interesting finding of this latter study was that NOLD was similar in the control subjects infused with saline and in those fed the protein-free meal, indicating that nonprotein energy sources were ineffective in stimulating postprandial whole body protein synthesis [33].

With regard to postprandial splanchnic protein synthesis, ingestion of a mixed meal of about 1000 kcal results in a stimulation of albumin synthesis by \(\sim 40\%\) [unpublished data] (Fig. 2), suggesting that hepatic protein synthesis responds acutely to nutrient ingestion. The increase in total (that is, intravascular plus extravascular) albumin synthesis would account for \(\sim 35\%\) of the increase in whole body protein synthesis (Fig. 2), thus representing a consistent fraction of the postprandial protein anabolic effect in the fed state. These data are in close agreement with previously published studies [19, 33–35].

Dietary proteins are also important for postprandial stimulation of albumin synthesis [33, 34]. Indeed, when isoenergetic meals with or without amino acids are given, the increase in postprandial albumin FSR following a meal without amino acids is nearly half that following a complete meal [33], despite a comparable increase in insulin. The increase in albumin synthesis with the...
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amino acid-deprived meal could thus be attributed to the postprandial increase in insulin, which has been shown to stimulate albumin synthesis [36]. Isoenergetic meals with or without proteins (~18% of total energy), given at a rate of ~1.5 kcal/kg/h for 10 h, were associated with a 70% increase in albumin synthesis over that observed with a protein-free diet [37], further underlying the role of dietary amino acids in the postprandial stimulation of albumin synthesis. On the other hand, no effects of intravenous nutrients on albumin synthesis were observed in humans [37], suggesting that the oral route of amino acid administration is the key to the stimulation of albumin synthesis.

By using the isotope incorporation method, feeding did not increase duodenal mucosal protein synthesis in humans [24], in comparison with a control group subjected to a short-term fast (~36 h). These data suggest that hepatic protein synthesis responds more than small bowel protein synthesis to oral nutrients. This finding, however, is in contrast with other animal data [28, 29, 38] (Fig. 1). These contrasting results may be related to differences in the techniques used, to individual animal species, or to age. For example, protein synthesis in the jejunum is less responsive to feeding in old than in young pigs [39]. The role of individual amino acids, such as glutamine, appears to be important in the stimulation of gut protein synthesis [30]. Despite these inconsistencies in the experimental data, it is commonly assumed that oral feeding is necessary to prevent atrophy of the intestinal mucosa [30].

Fig. 2. Effects of mixed meal ingestion on whole body protein synthesis (PS, g/h; left panel), albumin synthesis (g/h; middle panel), and the percentage contribution of albumin to whole body (WB) protein synthesis (PS, right panel) in healthy human subjects. Albumin synthesis was estimated as the sum of both the intravascular and the extravascular pool. (From reference 3 and unpublished results).
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Finally, splanchnic protein metabolism appears to be strongly related to oxygen consumption and energy expenditure. Indeed, nutrient ingestion – mostly protein – increases both whole body and splanchnic oxygen consumption (Fig. 3) [40–42]. In the first hour after the meal, the whole body increase is due mainly to that of splanchnic organs. This increase is probably linked to the stimulation of postprandial splanchnic protein synthesis.

References

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**Discussion**

*Dr. Young:* You showed that the fractional rate of protein synthesis in the colon was actually higher than in the small intestine. That would seem to contradict the point that Dr. Reeds made, that protein synthesis in the colon is relatively sluggish. Would you comment?

*Dr. Tessari:* You are right. Those data with regard to colon reflect older studies, and are not representative of the most up-to-date assessments of intestinal FSR.

*Dr. Young:* One other point is that your protein synthesis rate in the kidney amounted to about 0.5 g/h, which would make the FSR per day about 20%, as I recall or calculate. That’s a very high rate of protein synthesis in the kidney.

*Dr. Tessari:* Those data were obtained from arteriovenous differences of unlabeled and labeled leucine, but as you know the kidney is very active in filtering and reabsorbing proteins, mostly peptides. These peptides may be degraded within the kidney and their amino acids be released in the renal vein as free, and this will artificially inflate our estimates of protein turnover. We still don’t have a method of accurately measuring protein synthesis in the kidney.

*Dr. Jackson:* I have two points to make. One follows on from Dr. Young’s question relating to the fractional synthesis rate of protein in the colon. It is possible that differences in published values might reflect bacterial activity in the colon. Secondly, you made the point in your talk that when you sum the rates of protein synthesis for
individual proteins, they appear to be substantially greater than the measured total protein synthesis rate. I wonder whether you would like to offer us an explanation of why that difference might be? Is it that we are underestimating the total protein synthetic rate or overestimating the synthetic rate of individual proteins, or do the methods just not measure the same thing at all?

Dr. Tessari: I don’t have an answer to that yet.

Dr. Wernerman: I assume you used a constant infusion when measuring albumin, but I wonder whether the length of time over which you made the measurements might have resulted in an underestimation of the contribution of the fast turnover proteins.

Dr. Tessari: We fed the meal for 4 h and used the data in the last hour, so we waited for about 3 h to reach a steady state in the plasma.

Dr. Lundholm: Another problem considering albumin synthesis is purification of albumin. How did you purify your albumin when you did the measurement?

Dr. Tessari: We did a differential precipitation. First of all we removed the immuno-globulins with ammonium chloride, and then we used differential extraction with ethanol in acid, so we removed any contaminat (i.e. free amino acids) from plasma, which could interfere with the specific activity. Then, we checked the albumin band with SDS-PAGE electrophoresis before the start of the studies, and showed that there was a single band. So this method was used for all the studies.

Dr. Millward: You showed us some data on leucine and phenylalanine comparisons from your own lab. Can you remind me, was that with the deuterated phenylalanine model?

Dr. Tessari: Yes, the phenylalanine data of splanchnic kinetics were obtained with a D5-phenylalanine and a D2-tyrosine infusion and priming the D4-tyrosine pool.

Dr. Millward: The issue is then the way in which you calculate the hydroxylation rate and the actual appearance rates of phenylalanine. You may recall a couple of years back that we published a paper where we attempted to determine the magnitude of the error that creeps in when you use enrichment of the tyrosine and the phenylalanine in the plasma, compared with what you might predict it to be in the intracellular pool [1]. We showed that the hydroxylation rate may well be out by a factor of 2, and that the appearance rate may well be out by 20 or 30%. Have you tried making those adjustments to your data to see whether this influences the difference that you get between leucine and phenylalanine?

Dr. Tessari: That is a very nice suggestion. We didn’t make those calculations. You may be right. If phenylalanine hydroxylation across the splanchnic area is higher than what we have measured, protein synthesis will be lower and so there might be no net positive balance across the splanchnic bed.

Dr. Young: The increase in albumin synthesis is interesting. Could you speculate why it occurs? I recall Morey Haymond’s proposal that the increase in albumin synthesis during the absorptive period was a way in which amino acids might be retained for subsequent utilization during the postabsorptive period.

Dr. Tessari: I believe that this is a very good interpretation. After meals the liver increases the production of albumin, which is used as an export protein to bring amino acids to the periphery. In the postabsorptive state about 10% of the hepatic protein synthetic machinery is devoted to albumin synthesis on average over 24 h, but this can increase to 40–50% under certain conditions, such as meal stimulation. The second point is that I tried to determine the increase of dietary leucine-derived protein synthesis in the splanchnic bed in terms of grams per hour increase in albumin synthesis. I calculated that about 50% of dietary leucine was used at first pass in the splanchnic area to produce albumin. This 50% ratio is very close to the ratio that Cayol et al. [2] published. They concluded that about 50% of the dietary leucine taken up by the splanchnic area at first pass is incorporated into albumin. So I think that in the postprandial state albumin
synthesis is remarkable and it accounts for a large portion of the splanchnic uptake of dietary amino acids.

Dr. Déchelotte: We presented data recently showing that in subjects in whom protein turnover was enhanced by glucocorticoids, glutamine could enhance gut FSR by about 40%, which was statistically significant; and with an even greater (pharmacological) load of glutamine, gut FSR was increased by about 80–100%, depending on the route used for the tracer infusion (intravenous or intraduodenal) [3]. We would like to get an idea of the net protein equation in the gut. What in your view is the best way to study this in humans?

Dr. Tessari: One way might be to use Apoβ-48, which is a gut-produced protein. It might be possible to obtain a steady-state enrichment of this protein and determine the intracellular intestinal enrichment of the precursor pool in the fed state.

Dr. Beaufrère: Could you comment on the role of protein breakdown? I believe we tend to think in terms of protein synthesis just because we know how to measure it.

Dr. Tessari: Of course that is a very important point, but I don’t believe we yet have an established model to measure fractional protein breakdown in the body.

Dr. Reeds: I’m glad you’ve raised that, because I, like everybody else, has measured synthesis and tried to measure growth, which is the more difficult thing to do in some respects, and then back-calculated degradation. Doug Burrin and I are very reluctantly coming to the conclusion that protein degradation in the small intestinal mucosa may be a much more important regulator of mucosal mass than protein synthesis itself. Dr. Burrin has done some GLP2 infusions in newborns, where he’s got a 40% increase in gut mass, no change in the depth of the crypts, longer villi, and no change in protein synthesis whatsoever. That has to reflect degradation and apoptosis. We found much the same thing in older animals, particularly in the ileum and in relation to glucocorticoid treatment.

Dr. Young: Dr. Reeds, what dietary factors might promote a reduction in protein breakdown in the gut?

Dr. Reeds: As, in my opinion, we don’t really know anything about the regulation of gut growth at a mechanistic level, I can’t say. But if we use portal blood flow as a way of inferring that there’s been a rapid change in metabolism, then despite the fact that dietary carbohydrate seems to play little immediate role in gut metabolism, it appears that carbohydrate is the most potent stimulus to gut metabolism. We’ve certainly found in some GLP2 secretion studies that dietary carbohydrate is a better secretagog for GLP2, which appears to be a small intestinal growth stimulator.

Dr. Millward: It’s very interesting that when you consider the mechanisms and mediators of the inhibition of proteolysis, leucine is re-emerging as an important specific mediator here. Indeed Dr. Young presented data on the role of leucine in the regulation of transcription and translation. Leucine is not only the most abundant amino acid in body protein and therefore a very important constituent of feeds, but may also be a key regulator.

Dr. Tessari: I agree that leucine may be important in suppressing protein degradation, although in vivo data are not so striking. There are leucine infusion studies in which the leucine that was given increased oxidation and slightly increased protein synthesis but had no effect in protein degradation [4–6].

Dr. Millward: I think there may be an important interaction with insulin and of course in the postprandial state one always has the initial insulin effect, over which one adds the additional influence of amino acids, and so looking at a response to leucine on its own, in the absence of a priming of the system first with insulin, you may well miss the effect.

Dr. Young: Dr. Tessari, you showed some very nice relations between splanchnic protein synthesis and oxygen consumption. It was my understanding that following a meal, the increase in oxygen consumption by the liver was largely due to catabolism of
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amino acids and to the gluconeogenesis that occurs during that period of the fed state. Would you care to comment on the extent to which protein synthesis versus amino acid catabolism accounts for major changes in oxygen consumption in the liver during the absorptive period?

Dr. Tessari: From published reports it appears that the deposition of 1 g of protein requires two- to fourfold more energy than is theoretically needed to synthesize that amount of protein. This would suggest that there are other energy-requiring processes going on. Part of this energy might well come also from amino acid catabolism, which on turn could be linked to gluconeogenesis. Postprandial gluconeogenesis might be one of the major processes that require energy in parallel with a protein deposition after a meal.

References