Contribution of plasma proteins to splanchnic and total anabolic utilization of dietary nitrogen in humans

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Submitted 30 October 2002; accepted in final form 11 March 2003

Fouillet, Hélène, Claire Gaudichon, Cécile Bos, François Mariotti, and Daniel Tomé. Contribution of plasma proteins to splanchnic and total anabolic utilization of dietary nitrogen in humans. Am J Physiol Endocrinol Metab 285: E88–E97, 2003. First published March 18, 2003; 10.1152/ajpendo.00469.2002.—Splanchnic tissues are largely involved in the postprandial utilization of dietary amino acids, but little is yet known, particularly in humans, about the relative contributions of different splanchnic protein pools to splanchnic and total postprandial anabolism. Our aim was to develop a compartmental model that could distinguish dietary nitrogen (N) incorporation among splanchnic constitutive, plasma (splanchnic exported), and peripheral proteins after a mixed-protein meal in humans. Eight healthy subjects were fed a single mixed meal containing 15N-labeled soy protein, and dietary N postprandial kinetics were measured in plasma free amino acids, proteins, and urea and urinary urea and ammonia. These experimental data and others previously obtained for dietary N kinetics in ileal effluents under similar experimental conditions were used to develop the compartmental model. Six hours after the mixed-meal ingestion, 31.5, 7.5, and 21% of ingested N were predicted to be incorporated into splanchnic constitutive, plasma (splanchnic exported), and peripheral proteins, respectively. The contribution of splanchnic exported proteins to total splanchnic anabolism from dietary N was predicted to be ~19% and to remain steady throughout the simulation period. Model behavior and its predictions were strongly in line with current knowledge of the system and the scarce, specific data available in the literature. This model provides the first data concerning the anabolism of splanchnic constitutive proteins in the nonsteady postprandial state in humans. By use of only slightly invasive techniques, this model could help to assess how the splanchnic anabolism is modulated under different nutritional or pathophysiological conditions in humans.

protein metabolism; postprandial interorgan metabolism; mathematical model; parameter estimation; healthy humans

AFTER INGESTION, amino acids (AA) released by the gastrointestinal digestion of dietary proteins are absorbed through the intestine and then subjected to sequential anabolic sequestration into the splanchnic (i.e., intestinal and hepatic) and peripheral protein pools. At the same time, a proportion of the AA absorbed is deaminated in the liver, the nitrogen (N) then being excreted in urine. These anabolic and catabolic pathways are involved in controlling the availability of dietary N throughout the body, and the nutritional efficacy of a protein meal is related mainly to the relative orientation of dietary AA between these processes.

A growing body of evidence indicates that the splanchnic handling of dietary AA is a critical stage in their postprandial metabolic orientation. Because the gut and liver intervene in AA transfer to the peripheral zone and exhibit a high protein turnover, splanchnic tissues are thought to have a major impact on both the peripheral bioavailability of dietary AA and the overall postprandial utilization of AA for anabolism. There is indeed an important splanchnic uptake of dietary AA during the early postprandial phase, which modulates their delivery to peripheral tissues (24, 34, 47, 59). Transient postprandial sequestration of dietary AA in the splanchnic tissues is achieved via the incorporation of dietary N into two main protein pools, which include both constitutive and exported proteins (synthesized by the splanchnic tissues and exported to the plasma). For instance, the synthesis of albumin (the most abundant plasma protein), which takes place exclusively in the liver, has been reported to be regulated by insulin and enteral AA delivery, levels of which rise dramatically after the ingestion of a mixed meal (16, 17, 30, 52, 54). The acute anabolic effect of a mixed meal thus occurs primarily in the splanchnic area (16, 17, 25, 38, 44, 49, 52, 54), whereas muscle protein synthesis makes only a minor contribution to the whole body anabolic response despite the large mass of muscle (37, 56). It is believed that the splanchnic anabolic processes allow for the sparing of dietary N from deamination through the temporary “storage” of ingested AA in the labile splanchnic protein pool (17, 45, 48, 50, 57) while simultaneously buffering the peripheral tissues from excessive changes in free AA concentrations (1, 45, 47). Despite recent advances in our understanding of splanchnic interorgan transfer and the metabolism of dietary AA in the fed state, thanks to the use of animal models (38, 39, 48–50), little is still known in humans about the relative contributions of the different splanchnic protein pools to postprandial anabolism. This question is of crucial importance to under-

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standing the significance of these complex postprandial processes, which have many clinical implications.

This work aimed to develop a predictive modeling tool that would allow for the determination of the contribution of plasma proteins to the splanchnic and whole body anabolic utilization of dietary N in humans. We previously developed a compartmental model that specifically follows ingested N in the postprandial nonsteady state and simulates its incorporation into total splanchnic and peripheral proteins after the ingestion of a single protein meal in humans (26). In the present work, our objectives were to modify this model structure so as to distinguish between splanchnic exported and constitutive proteins by use of experimental data obtained in different pools, including plasma proteins, after the ingestion of mixed soy protein meals in healthy humans. The resulting expanded model will enable the determination of the relative contributions of exported and constitutive splanchnic proteins to postprandial anabolism from dietary N in humans and, hence, the study of nutritional or physiopathological modulation in this area.

MATERIALS AND METHODS

Collection of experimental data. Eight healthy subjects, aged 29 ± 6 yr and with a body mass index 21.4 ± 2.5 kg/m² were adapted for 7 days to a standard diet providing 1 g·kg⁻¹·day⁻¹ protein and 138 kJ·kg⁻¹·day⁻¹ (54.3% of energy as carbohydrate, 33.3% as fat, and 12.3% as protein). At the end of this period, the subjects were admitted to the hospital after an overnight fast and given a single mixed meal supplying one-third of their previous daily intake, containing an average of 22.4 g of ^15N uniformly labeled soy protein (Nx5.52), 90 g of carbohydrate (25% as sucrose and 75% as maltodextrins), and 22 g of sunflower oil mixed with water up to 500 ml. The volunteers ingested their experimental meal within 10 min. The subjects were studied during the 8-h postprandial phase, when total urine was collected every 2 h and blood samples were drawn hourly using a catheter inserted in a forearm vein. Urine was measured for volume and then stored at +4°C before analysis. Aliquots of serum or plasma were collected and stored at −20°C until analysis. Total body water was determined using multiple-frequency bioimpedance analysis (Analytocor 5w; Spengler, Cachan, France) in each subject.

Serum protein was precipitated from 800 µl of serum by the addition of 40 µl of a sulfosalicylic solution (1 g/ml). After 1 h of precipitation, the protein fraction was separated from the supernatant by centrifugation (20 min at 3,000 g). The urea and AA fractions in plasma and the ammonia and urea fractions in urine were extracted using cation-exchange resins as described previously (35). Urea and ammonia in the samples were determined on clinical analyzers (Dimension Automate; Dupont de Nemours, Les Ulis, France and Kone Automate; Kone, Evry, France, respectively). Plasma AA were analyzed on an HPLC system (AminoSystem 2500; Bio-tek Instruments, St Quentin en Yvelines, France) combined with a postcolumn ninhydrin derivatization. The total N content in the plasma protein fraction was determined using an elemental analyzer (NA 1500 series 2; Fisons Instruments, Manchester, UK) according to the Dumas method, with atropine as a standard. ^15N enrichments in samples were determined by isotope ratio mass spectrometry (Optima; Fisons Instruments). A calibrated N gas was used as the reference to derive the ^15N-to-^14N ratio.

Dietary N pools were quantified in plasma (urea, AA, and protein) and urine (urea and ammonia) using isotope dilution equations, which have been described in detail elsewhere (35). The dietary N content of each sampled pool was determined kinetically for each subject, and all data sets were expressed as a percentage of ingested N. Because the kinetics of dietary N were not determined in ileal effluents during this experiment, we used analogous results from a previously reported study, wherein 10 healthy subjects equipped with an ileal tube had ingested a mixed soy protein meal with the same energy and protein content (35). However, the entire nonprotein energy content had been given as carbohydrates in that meal, whereas one-third was substituted by fat in the present experiment. We did not repeat the ileal sampling in the present experiment, because we knew from different data that the kinetics of dietary N appearance in ileal effluents are hardly modified by the nature of the nonprotein energy content of the meal. For example, it has previously been shown in minipigs fed two isoenergetic meals with different protein content (carbohydrate-protein ratio of 80:20 and 20:80), that the flow of protein into the jejunum is the same whatever the nature of the nonprotein energy content of the meal (58). The mean data for dietary N kinetics in ileal effluents, expressed as a percentage of ingested N, were used to complete individual data during the current experiment. Both protocols were approved by the Institutional Review Board of Saint-Germain-en-Laye Hospital (Saint-Germain-en-Laye, France), and informed consent was obtained from each subject.

Selection of a compartment model based on a previously developed linear model. A linear compartmental model had previously been developed using experimental data obtained after the ingestion of a single, pure milk protein meal in humans (26). This model comprised 11 compartments representing distinct amounts of dietary N and 15 different pathways of exchange, each characterized by a constant diffusion coefficient k_ij, representing the fraction of dietary N in compartment j transferred to compartment i per unit time. The model structure included three subsystems: the gastrointestinal tract and the deamination and retention subsystems. This model has successfully been cross-validated using experimental data obtained after the ingestion of various mixed-protein meals (25, 27). By confronting the model with data obtained after the ingestion of milk protein with additional sucrose or fat (25) or after the ingestion of soy protein with sucrose (27), it has been proved that this model is capable of discriminating between different nutritional conditions. However, if sucrose was present in the meal, and whatever the protein ingested, we found slight but systematic deviations between experimental data and model predictions for ileal effluents. This suggests that the model may be too simple to fit the data accurately under these particular nutritional conditions (14). The delay in intestinal transit in the presence of sucrose may therefore require at least one more compartment in the gastrointestinal tract subsystem to better fit the ileal data (25, 27).

In the present work, we modified this basic model so as to distinguish between dietary N incorporated into splanchnic constitutive and exported proteins after a mixed-protein meal. Indeed, it was not possible to modify the gastrointestinal tract subsystem structure by adding one or more compartments representing dietary N in the intestinal lumen so as to fully adapt the model to the case of mixed meal ingestion. Furthermore, to individualize the plasma proteins now being sampled, we had to modify the retention subsystem structure.
by splitting the splanchnic protein compartment of the basic model into one constitutive and one exported compartment. The methods we used to identify the adequate structure for the expanded model incarnated the principle of parsimony and consisted in testing the goodness of fit of different models of increasing order and retaining the simplest structure that adequately fitted the data vs. higher-order models that did not significantly improve the fit (15, 26). To achieve this, candidate models were all confronted with the experimental data using SIMUSOLV software (20) and then discriminated using the Akaike and the Schwarz criteria (15, 32) and the likelihood ratio test (46).

Parameter estimation and sensitivity analysis. SIMUSOLV software (20) was used to estimate those parameter values that would produce the closest model predictions by adjusting rate constant values until the model predictions fitted the data for all sampled compartments simultaneously. The objective function iteratively maximized during the parameter estimation process under SIMUSOLV was the log of the likelihood function (20, 26). Different values for initial parameter estimates were tested to ensure that final parameter estimates provided the best possible fit and not a local optimum. Each candidate model was quantified for the mean of individual data by means of parameter estimation, and the selected model was also quantified for each subject.

Sensitivity analysis of the model was performed by evaluating the effect of a 1% change in parameter value on the prediction of a variable response, i.e., by calculating a sensitivity coefficient for each pair: δ(model response)/δ(model parameters). However, so as to eliminate the bias caused by the magnitude in parameter values, sensitivity coefficients were log-normalized and calculated using the direct derivative method under SIMUSOLV (20). Sensitivity analysis was performed on the parameter estimate values obtained after optimization using the mean of individual data by evaluating their influence on the model responses for each compartment.

RESULTS

Structural modeling and theoretical identifiability. The model selected consists of 13 compartments and 19 different pathways of exchange between these compartments (Fig. 1). The gastrointestinal tract subsystem consists of four compartments representing dietary N in the stomach (G), dietary N in the lumen of the proximal (IL1) and distal (IL2) small intestine, and dietary N at entry into the colon (E), respectively. Dietary N is considered to enter the first compartment (G) as a bolus. The deamination subsystem consists of three compartments representing dietary N in body urea (BU), dietary N in urinary urea (UU), and dietary N in urinary ammonia (UA). The retention subsystem comprises six compartments representing dietary N in splanchnic free AA (SA), dietary N in splanchnic constitutive proteins (SCP), dietary N in splanchnic exported proteins (SEP), dietary N in plasma free AA (PL), dietary N in peripheral free AA (PA), and dietary N in peripheral proteins (PP). The synthesis pathway from SA to SEP integrates a variable delay that may account for the time interval between the synthesis of plasma proteins and their appearance into the blood.

This model was selected from among different candidates, all of which had structures with a firm physiological basis. In particular, the chosen model was compared with two other candidate models of increasing order used to determine the optimum structure for the gastrointestinal subsystem. Compared with the structure selected, the lower-order model was characterized by an absence of compartment IL2, whereas the higher-order model integrated an additional compartment (IL3) between IL2 and E, in line with the classical method for modeling the gastrointestinal tract by using a catenary structure (7). Similarly, to determine the optimum structure for the retention subsystem, the chosen model was compared with various candidate models and in particular with two other nested models. Compared with the selected structure, the lower-order model was characterized by an absence of the delay component between SA and SEP, whereas the higher-order model included an additional degradation pathway from SEP to PA. The structure that was finally selected was the minimum necessary to fit all sampled compartments simultaneously. The results reported in Table 1 show that the Akaike and the Schwarz criteria and ratio tests all led to the selection of the chosen model, which significantly improved the fit by comparison with lower-order models, there being no significant improvement in the fit between the chosen model and higher-order models.

By use of the recently developed software package GLOBI2, which enables assessment of the theoretical identifiability of linear compartmental models (2), the basic model had previously been shown to be uniquely identifiable (26); i.e., theoretically, all its parameters had a unique solution in the ideal context of an error-free compartmental model structure with noise-free and continuous time measurements. In the present work, we could not formally test the a priori identifiability of the expanded model, because GLOBI2 only works for models with fewer than 12 compartments (2). Although the a priori identifiability of the expanded model has not been demonstrated and may not be demonstrable for practical reasons, the model structure and experimental design met all of the necessary topological conditions for identifiability (2). When real data were considered, the results of identifiability concerning the expanded model fell into the realm of numerical identifiability.

Parameter estimation and numerical validation. The model fitted all subjects satisfactorily, but a better fit was obtained for each compartment when the mean of individual data was used. The distribution of parameter estimates did not differ significantly when obtained using the mean of individually fitted parameters or when the mean of individual data was directly fitted (Wilcoxon matched pairs signed ranks test, two-tailed P value ≥ 0.95). The optimization criteria and parameter estimates obtained after optimization using the mean of individual data are given in Tables 2 and 3. Parameter estimation required validation to ensure that parameters were estimated with sufficient confidence to provide meaningful information about the system under study. The numerical identifiability of the model was tested successively by checking the goodness of fit, the randomness of residual errors, and
the reliability of parameter estimates (14, 26, 32, 46). The goodness of fit appeared to be highly acceptable from visual inspection of a plot of model predictions vs. experimental data (Fig. 2). The standardized residuals of sampled compartments were consistent with the underlying assumptions of both the normality and randomness of the data error distribution involved in optimization, as formally tested by an analysis of residuals (results not shown). The reliability of parameter estimates was judged as highly acceptable, since the parameters were estimated with very good precision (all coefficients of variation for fitted parameters being <28%, as shown in Table 3).

**Sensitivity analysis.** As previously reported for the basic model (26, 27), the results of the sensitivity analysis, which enabled identification of those parameters with the greatest influence on the system, agreed with the model structure and our knowledge of system behavior. Whatever the compartment, the gastric emptying rate constant ($k_{2,1}$), and to a lesser extent the rate of absorption in the proximal intestine ($k_{5,3}$) and to a lesser extent the rate of absorption in the distal intestine ($k_{5,3}$) exhibited considerable initial influence that then slowly declined, whereas the rate of absorption in the distal intestine ($k_{5,3}$) exhibited a weaker influence that increased over time, finally reaching that of $k_{5,2}$. Moreover, with respect to the influence of parameters on the regional protein pools (i.e., SCP, SEP, and PP), the rates of delivery to the periphery ($k_{8,5}$) and transfer to body urea ($k_{11,5}$), splanchnic constitutive ($k_{8,5}$) and exported ($k_{9,5}$) proteins were additionally identified as important governing parameters, as had previously been reported for their homologs in the basic model (26, 27). SCP was most positively sensitive to variations in $k_{8,5}$ and negatively sensitive to those in $k_{6,5}$, $k_{11,5}$, and $k_{9,5}$, in descending order, whereas SEP was most positively sensitive to variations in $k_{9,5}$ and negatively sensitive...
to those in $k_{8,5}$, $k_{6,5}$, and $k_{11,5}$, in descending order. Moreover, PP was positively sensitive to variations in $k_{6,5}$, and $k_{10,7}$, in descending order, and negatively to those in $k_{8,5}$, $k_{11,5}$, and $k_{9,5}$, in descending order.

Predicted kinetics of dietary N absorption and transfer to splanchnic and peripheral organs. The model enabled simulation of the successive transfer of dietary N between the different compartments (Fig. 3). The model simulated a dietary N gastric-emptying halftime of 64 min. The ileal digestibility of dietary N reached 91% at 8 h after the meal, and 80% of dietary N absorption was predicted to occur in the upper part of the gastrointestinal tract, i.e., in IL1. Dietary N appeared rapidly and transiently in the splanchnic free AA compartment (SA), with a peak reaching 6% of ingested N 1 h and 30 min after the ingestion of the meal. Dietary N incorporation into both constitutive (SCP) and exported (SEP) splanchnic proteins occurred consecutively, reaching values of 31.5 and 7.5% of ingested N 6 h after the meal, respectively. In the peripheral area, the appearance of dietary N in free AA (PA) peaked at ~10% of ingested N, 3 h and 10 min after the meal. Total anabolism (PP) and retention (PA + PP) in the peripheral area, which were still increasing during the simulation period, amounted to 21 and 27%, respectively, of ingested N 6 h after the meal.

DISCUSSION

During this work, we developed a new compartmental model providing a predictive tool for the noninvasive determination of dietary N kinetics in the postprandial nonsteady state, including its absorption, elimination, and incorporation into splanchnic constitutive, splanchnic exported, and peripheral proteins.

The model was built using experimental data concerning dietary N postprandial kinetics determined in the intestine, blood, and urine after the bolus ingestion of a mixed soy protein meal in humans. Parsimonious modeling was applied to the choice of the model structure so that it would be the minimum necessary to fit the sampled compartments. The model structure that best fitted the plasma protein data integrated a synthesis pathway from splanchnic free AA to splanchnic

Table 3. Parameter estimates and their precision

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<tr>
<th>Parameter Estimates</th>
<th>CV</th>
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<tr>
<td>$k_{2,1}$</td>
<td>1.08E-02</td>
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<tr>
<td>$k_{2,5}$</td>
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<td>$k_{12,11}$</td>
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</tr>
<tr>
<td>$k_{13,5}$</td>
<td>2.33E-04</td>
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<tr>
<td>LAG</td>
<td>31.0</td>
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$k_{ij}$ Parameter estimate values in min$^{-1}$. LAG, delay value in min. Optimization was performed using the mean of individual data. SDs expressed as coefficients of variation (CVs) [SD value] x 100. Those parameters for which no CV is reported were maintained constant throughout the final step of optimization due to multicolinearity features.
exported plasma proteins with an additional variable delay. This delay may account for the secretion time of plasma proteins, i.e., the time interval between the synthesis of plasma proteins and their appearance in the blood (12). This delay was optimized during parameter estimation to a value of $31 \pm 4$ min, which is in striking agreement with previously reported values for the secretion time of albumin (the most abundant plasma protein) in the fed state in humans ($32\text{–}33$ min) (30). Furthermore, the presence of additional degradation pathways from plasma proteins to either splanchnic or peripheral free AA was tested and rejected on grounds of parsimony. The long biological half-life of albumin ($\approx 20$ days) may explain the fact that the degradation of newly synthesized plasma proteins from dietary N could be neglected throughout the simulation period ($12$ h after the meal). Nevertheless, a degradation pathway from plasma proteins may have accounted for the rapid degradation of newly synthesized plasma proteins with a rapid turnover [e.g., apolipoprotein B (apoB)]. The fact that the modeling process gave rise to a model structure that neglected the degradation suggests that proteins with the slowest turnover (such as albumin or fibrinogen) dominate quantitatively the kinetics of newly synthesized plasma proteins from dietary N. This idea is in line with previous data concerning the kinetics of these different plasma proteins in humans (18), where apoB-100, despite a high fractional synthesis rate, made a minor contribution to the total plasma proteins synthesized ($\approx 10\%$ of that of albumin plus fibrinogen) when expressed in absolute synthesis rates. However, the

Fig. 2. Fits obtained after optimization using the mean of individual data: observed vs. predicted values for dietary N kinetics in each sampled compartment: ileal effluents (A), body urea (B), plasma free AA (C), urinary urea (D), plasma proteins (E), and urinary ammonia (F). Experimental data (points) and model predictions (lines) are expressed as %ingested N over time. Each observed mean is plotted by value $\pm 2$ SD, with SD being determined during optimization.
purpose of the present model was not to describe the intrinsic complexity of the plasma protein system, which can be addressed only if the model is developed further using appropriate experimental data (i.e., dietary N incorporation into different plasma proteins). Application of the model to either a longer period of time or to total N (i.e., both dietary and endogenous N) would probably require the inclusion of degradation pathways from plasma proteins in the model structure.

The plausibility and physiological relevance of the model are strongly supported by the consistency of its predictions with respect to our current knowledge of the system. The model predictions in terms of the gastric-emptying half-time, flow rates of absorption, and net absorption from the different intestinal lumen compartments are strikingly in line with current knowledge of gastrointestinal kinetics (3, 8, 21, 29, 60), as summarized in Table 4. For instance, ~80% of dietary N absorption was predicted to occur in the upper part of the gastrointestinal tract, in line with the idea that dietary N is principally absorbed in the proximal part of the small intestine (28, 29, 60). Furthermore, the model predicted a predominant splanchnic uptake of dietary N during the early postprandial phase that modulated the delivery of dietary AA to peripheral tissues, consistent with our current knowledge of the system (1, 11, 47). The model made it possible to determine that, 6 h after the ingestion of a mixed soy protein meal, 31.5, 7.5, and 21% of ingested N were incorporated into splanchnic constitutive, splanchnic exported, and peripheral proteins, respectively. As far as whole splanchnic and peripheral anabolisms after a mixed soy protein meal are concerned, these results were found to be very consistent with those obtained using a previously developed model that had not been able to distinguish between the constitutive and exported parts of splanchnic proteins (27). In addition, and as shown in Table 5, model predictions for the regional metabolism of dietary N were validated in the light of findings available in the literature regarding the whole splanchnic (9, 13, 19, 31, 49, 50) and peripheral (11, 22, 38, 39, 53, 55) metabolism. In contrast, current knowledge concerning splanchnic interorgan metabolism and anabolism in the different splanchnic protein pools, which has mostly been obtained from experiments in animals (19, 38, 39, 48–50), remains unclear. In humans, protein synthesis in gut tissues has been the subject of little investigation, particularly in the fed state (10), because of major technical and/or theoretical difficulties. Discrepancies between synthesis rates measured using different methods and tracers have been reported and emphasize the fact that absolute values should be considered with caution (10, 34). Similarly, very little study has been devoted to total liver protein synthesis in humans, because such investigations require direct access to liver tissues, thus raising technical difficulties and potential risks (5, 6, 30). For example, laparoscopic cholecystectomy, which might be considered the only ethically acceptable technique to sample liver tissue in healthy subjects, has been shown to depress liver protein synthesis (6). For these reasons, most of our knowledge concerning human liver protein synthesis originates from investigations concerning the synthesis of export proteins such as albumin and fibrinogen (16, 17, 30, 49). The major feature of the present model is that it allows simulation of dietary N incorporation into splanchnic constitutive proteins by use of data from plasma proteins.

The model predicted that the contribution of splanchnic exported proteins to total splanchnic anabolism was constant throughout the 12 postprandial hours, reaching ~19%. During the scarce studies conducted in
humans, the contribution of albumin synthesis to total liver protein synthesis has been found to be \(\sim 15\%\) (5), in line with previous reports in animals (4, 30, 41). We were also able to calculate the postprandial incorporation of dietary N into plasma proteins as a proportion of its incorporation into total splanchnic protein from the findings of other reports in animals. After the ingestion or administration of a mixed-protein meal, this value ranged from 12 to 22% in pigs (48–51) and from 28 to 30% in rats (38, 39), in line with the model predictions. Furthermore, because the contribution of splanchnic exported proteins to total splanchnic anabolism was found to be constant throughout the simulation period, the model predictions indicated that there was no selective stimulation of plasma protein synthesis with feeding (i.e., no preferential stimulation of the synthesis of plasma proteins compared with that of constitutive splanchnic proteins), thus providing the first confirmation in humans of the few data available in animals (30, 36). In the fed state in adult rats, albumin synthesis has indeed been shown to increase in line with the rest of liver protein synthesis, with albumin synthesis as a proportion of total liver protein synthesis being similar in fasted and fed animals (\(\sim 13\%\)) (30). However, some nutritional or pathophysiological states may induce a preferential stimulation of the synthesis of particular splanchnic proteins in humans. In rats, it has been shown that the postprandial contribution of plasma proteins to total splanchnic anabolism from dietary N was twice as high in rats receiving a high-protein meal for the first time than in rats adapted to a high-protein diet (38). Under situations of stress (trauma, surgery, burns, infection, cancer, etc.), when the synthesis of acute-phase proteins is markedly stimulated, it is not known what absolute and relative changes occur in the other component of splanchnic protein synthesis. Although there is increasing evidence in humans that albumin synthesis does not decrease during stress (23, 33), a major reduction in albumin synthesis relative to total liver protein synthesis has been observed in animals in different situations of inflammation, infection, or sepsis (4, 40, 42, 43). In humans, a compartmental analysis such as the one accomplished here would enable assessment of the

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<th>Table 4. Comparison of findings in the literature and model predictions concerning gastrointestinal kinetics of N</th>
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<td>Model predictions</td>
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<td>Findings in literature</td>
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Model predictions after ingestion of a mixed soy protein meal in humans. IL1 and IL2, dietary N in proximal and distal small intestine lumen, respectively. Gastric-emptying half-time was calculated as \(\ln(2)/k_{1,2}\). Contribution of IL1 to total absorption was calculated as absorption from IL1 divided by the total absorption from both IL1 and IL2. *Values are predictions at different times for comparison with corresponding literature values. \(^{b}\)Predictions at 300 min where mean flow of dietary N from G to IL1 was \(\sim 70\) mg protein/min. \(^{c}\)Values from the literature for gastrointestinal kinetics and absorption of dietary N after a protein load. \(^{d}\)Half-time of gastric emptying of proteins after a mixed-protein meal of 1,840 kJ in humans (with a ratio of nutrients close to that of our meal: 51% carbohydrate; 15% protein; 35% fat) (8). \(^{e}\)Gastrojejunal and jejunoileal absorption of dietary N over the first 140 min after a mixed soy protein meal in humans (3). \(^{f}\)Amount of protein absorbed by the proximal half of the small intestine compared to the maximum amount of protein absorbable 120 min after a load of 24 g of intact soy protein in fistulated dogs (60).

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<th>Table 5. Comparison of findings in the literature and model predictions concerning the regional metabolism of dietary N</th>
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<td>Extraction, %dose</td>
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Model predictions at 6 h after ingestion of a mixed soy protein meal in humans. Splanchnic extraction is calculated as the sum of dietary N splanchnic retention (SA + SCP + SEP) and deamination (BU + UU + UA) for comparison with data in the literature. Peripheral retention is calculated as the sum of dietary N incorporation into peripheral free AA and proteins (PA + PP). Anabolism is calculated as the amount of dietary N incorporated into proteins (SCP + SEP in the splanchnic bed or PP in the peripheral area). Peripheral protein synthesis efficiency of dietary N was calculated as the flux of its incorporation into protein divided by the flux of its appearance in the free AA pool, i.e., \((k_{10,7} \times PA)/(k_{7,4} \times PL + k_{7,10} \times PP)\). *Values from the literature after a load containing protein or AA, either with carbohydrate or in a mixed meal; \(^{b}\)for Leu in humans (9, 13, 31); \(^{c}\)for Phe in humans (9, 31); \(^{d}\)Average values for Leu, Lys, Phe, and Thr in piglets (49); \(^{e}\)for Phe in pigs (50); \(^{f}\)for Val and Phe in pigs (19); \(^{g}\)for BCAA in humans (22); \(^{h}\)for dietary proteins in humans (11); \(^{i}\)for dietary proteins in rats (38, 39); \(^{j}\)for Phe in humans (55); \(^{k}\)for Lys in humans (53).
29. Hunter KA, Ballmer PE, Anderson SE, Broom J, Garlick PJ, and McNurlan MA. Acute stimulation of albumin synthesis rate with oral meal feeding in healthy subjects measured using only slightly invasive techniques, i.e., avoiding biopsies in the splanchnic area.

In conclusion, our model can be used as a predictive tool to highlight the acute postprandial mechanisms occurring in tissues and regulating the dynamic transfer of dietary N between organs. This model provides us with a deeper insight into the cascade of transient and dynamic metabolic processes involved in controlling dietary N distribution throughout the body, which plays an important role in replenishing protein stores in the phase of protein gain. It would be interesting to develop the model further by integrating compartments representing endogenous AA and proteins so as to understand the repercussions of dietary N postprandial distribution on endogenous N metabolism. By use of experimental data on plasma proteins, the model developed here provides the first data concerning the anabolism of splanchnic constitutive proteins in the nonsteady postprandial state in humans. The model could usefully be confronted with other experimental data obtained under a variety of pathophysiological and nutritional states.

This work was supported by Danone (Paris, France). H. Fouillette is the recipient of a grant from ITCF (Paris, France) and the French Department of Research.

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