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Factors in the Regulation of Glutamate Metabolism

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The amino acids of the body are in a dynamic state in which input comes from the food in our dietary protein and output takes the form of excreted nitrogenous end-products. Between these two, intermediary metabolism of amino acids consists of reactions, many of which irreversibly remove the amino acids from the body pool. However, protein turnover is a major metabolic pathway in which the majority of amino acids used for incorporation into proteins are eventually returned to the free amino acid pool, except for a small proportion resulting from posttranslational modification, such as 3-methylhistidine and hydroxyproline, which are liberated by protein breakdown as derived amino acids and do not become available for reincorporation.

The purpose of this review is to analyze the metabolism of glutamic acid in order to identify some of the mechanisms regulating its abundance in the free amino acid pools of the body. Accordingly, this article begins by considering the amount of glutamic acid consumed daily, its absorption, and its fate as it passes through the intestinal wall. Next, the roles of glutamic acid and glutamine in the exchange of nitrogenous compounds between organs and tissues will be explored. Then, a picture of the magnitude of the pools of free glutamate in different body compartments, and the fluxes through them, will be described. Finally, the effects of certain hormones and various dietary factors on glutamate metabolism will be summarized.

Two factors impede the assembly of a detailed quantitative picture of the metabolism of glutamic acid. First, glutamine is converted to glutamic acid during the acid hydrolysis of food and tissue proteins prior to analysis, and, in consequence, the reported glutamic acid content of dietary and tissue proteins is therefore inflated through glutamine breakdown (7). Second, the central position of glutamic acid in nitrogen metabolism makes it virtually impossible on the basis of current data to compute the contributions of the various intracellular metabolic pathways to additions to or removal of glutamic acid. We shall therefore have to content ourselves with quantitation of glutamic acid and glutamine exchange between tissues and from dietary sources.

INTAKE AND ABSORPTION OF GLUTAMIC ACID

Glutamic and aspartic acid and their amines are major constituents of most proteins. As mentioned above, the amides are converted to the corresponding

dicarboxylic acids when the protein is hydrolyzed in strong acid preparatory to amino acid analysis (7), so that most tabulations for food protein composition provide *total* glutamic and aspartic acids, including the amides. From the amount of ammonia liberated by acid hydrolysis, an approximate estimate of the proportion as amides can be obtained. In the case of proteins of animal origin, this turns out to be about 50%, whereas for plant proteins this can be as high as 80% of the total dicarboxylic acid content (7). On this basis, liver has about 12% total glutamic acid and 9% total aspartic acid, whereas muscle contains about 16 and 10%, respectively, and wheat, 33 and 4% (7,27). These figures can be used to estimate the total dicarboxylic amino acid intake from the diet.

During this century, the average American daily protein intake of 100 g has changed little, despite that the sources of dietary protein have increasingly emphasized animal foods over cereal sources in this period (25). The analysis of the intake of individual amino acids shows that the eight essential amino acids account for 38 g of this daily protein consumption (25). Of the remaining 63 g of nonessential amino acids, total intake of glutamic acid is about 20 g and total intake of aspartic acid is some 8 g on the basis of the food protein composition given in the preceding paragraph. About 50% of these intakes are likely to be in the form of the corresponding amide.

Protein metabolism commences with digestion and absorption, areas in which interest has been renewed in recent years. As is well known, digestion of dietary protein is dependent on hydrolysis by gastric pepsin followed by the proteolytic enzymes secreted by the pancreas and by the intestinal mucosa. The secretion of proteolytic enzymes by the pancreas is known to be regulated by the presence of dietary protein in the gut contents (Fig. 1) through a system of feedback regulation of pancreatic enzyme secretion (16). The enzymes of digestion resolve the dietary proteins into small molecules for absorption through the mucosal cells of the small intestine. Although some dietary protein is hydrolyzed to free amino acids prior to absorption, small peptides have recently been shown to play a significant role in the assimilation of dietary protein. Nevertheless, because of the presence of peptide hydrolases in the brush border and cytosol of the mucosal cells (20), these peptides undergo hydrolysis to free amino acids as they enter the mucosal cells, and, in consequence, only free amino acids are transferred to the portal vein (Fig. 1).

Another significant area is the secretion of protein into the gut. This includes digestive enzymes added to the gut contents, and epithelial cells shed from the gut mucosa in the process of being replaced by cell division in the crypts at the base of the villi. The magnitude of this endogenous protein output into the gut lumen is controversial, perhaps amounting to some 70 g of protein (23). Together with the average of 100 g protein consumed by an adult on a Western-type diet, some 170 g protein would be provided for absorption. Since fecal nitrogen output is commonly equivalent to 10 g protein daily, the efficiency of digestion and absorption of both dietary and endogenous protein must normally be high (Fig. 1).

Extensive work has been done on the absorption of free amino acids by the

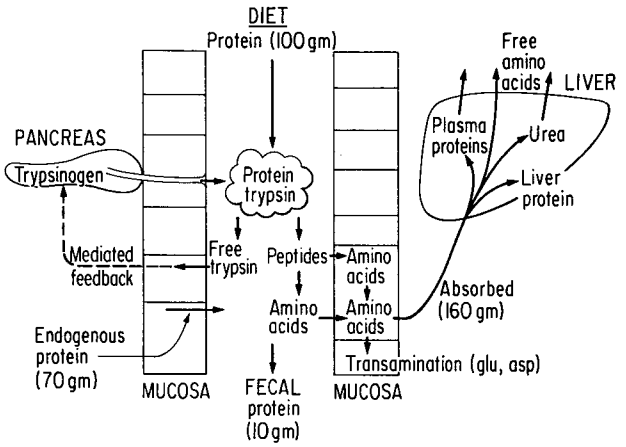

FIG. 1. The digestion of dietary protein, the shedding of protein into the gut, and the transport of amino acids and peptides across the mucosa. (From Crim and Munro, ref. 9.)

mucosa of the small intestine, where transport across the brush border is facilitated by three major carrier-mediated processes for neutral, dibasic, and diacidic amino acids (14). Studies made on rats by injecting mixtures of amino acids into loops of intestine show that the absorption of free aspartic acid and glutamic acid are much slower than that of other amino acids (14). This has been confirmed in humans (1) by using an intubation technique to perfuse the jejunum with equimolar amounts of free amino acids. Once more, the diacidic amino acids aspartic and glutamic acids were the slowest to be taken up. Silk et al. (36) extended this work to the absorption of peptides containing aspartic and glutamic acids. They confirmed that free glutamic acid and especially free aspartic acid are only slowly absorbed, whereas the same amino acids from peptides present in a tryptic digest of casein appeared to be better absorbed. However, as discussed above, much of the glutamic and aspartic acids estimated in acid hydrolysates are present in the original protein as amides. When Silk et al. (36) examined absorption of mixtures of equal proportions of the diacidic acids and their amides, the rate of uptake was equal to that of peptide glutamic and aspartic acids. The findings are thus equivocal regarding the more rapid uptake of aspartic and glutamic acids in peptide form, but do show that both dicarboxylic amino acids are at least as readily available from small peptides as in the form of free amino acids. Since the amino acids in peptide form do not generally appear in the portal blood, it can be assumed that absorbed peptides are efficiently hydrolyzed to free amino acids within the mucosal cells, where they join amino acids absorbed in the free form (Fig. 1).

The mucosal cells of the small intestine are active in the transamination of the dicarboxylic amino acids. Neame and Wiseman (30) demonstrated that absorbed glutamate is extensively transaminated with pyruvate to form alanine, which then

appears in increasing amounts in the portal blood. This has been confirmed by a variety of other studies (10,31,34,37,40). The concentrations of two transaminases, glutamate-oxalacetate and glutamate-pyruvate transaminase, have been examined in rat intestinal mucosal cell at various ages by Wen and Gershoff (38). In suckling rats, activity was low but rose steeply after weaning, provided that an adequate amount of the cofactor vitamin B_6 was present in the diet (Fig. 2).

The synthesis of alanine from glutamine and glutamate by mucosal cells and its release into the portal circulation has been extensively studied by Windmueller and Spaeth (39–41) and by Hanson and Parsons (17). Using an isolated preparation of rat small intestine perfused with blood, Windmueller and Spaeth (39) first showed

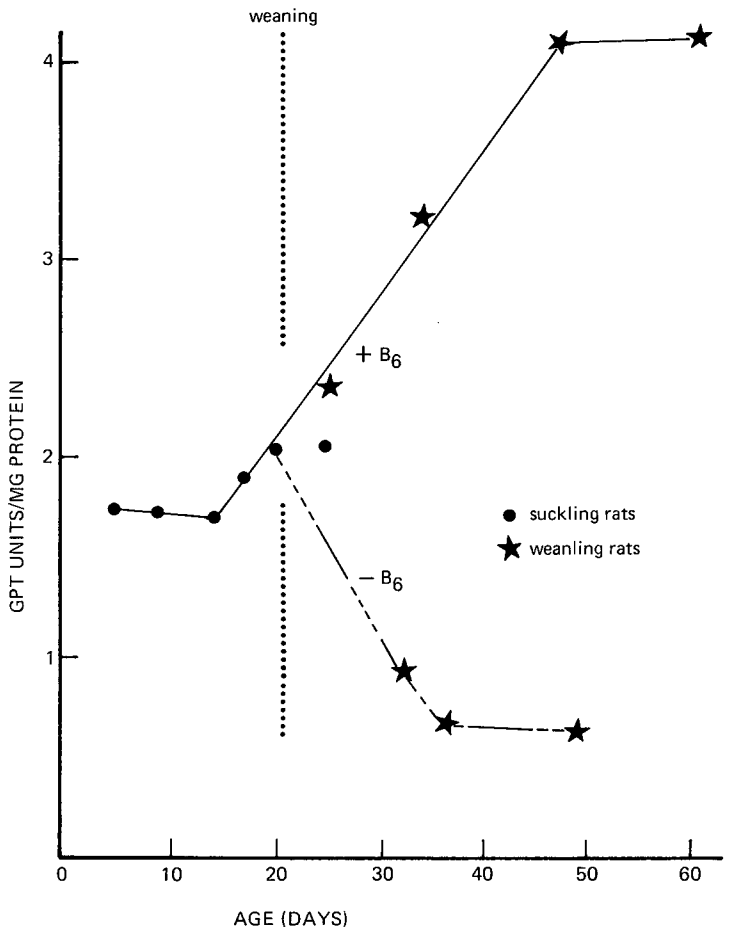

FIG. 2. Effect of age and of dietary vitamin B_6 on the glutamate-pyruvate transaminase content of the intestinal mucosa in suckling (•) and weanling (⋆) rats. (From Wen and Gershoff, ref. 38.)

that large amounts of glutamine were taken up from the incoming blood, and some one-third of its nitrogen could be accounted for as released alanine, whereas more than 50% of the carbon of the glutamine appeared as CO_2. In subsequent studies (40), they found that glutamate and glutamine administered by way of the lumen of the intestine underwent a similar fate. Thus, there is a single metabolic pool for glutamine entering the mucosal cell from the blood or from the lumen of the intestine. The first step in its utilization is hydrolysis to glutamate, through the action of glutaminase present in abundance in the mucosal cells, followed by transamination to yield alanine and other products of glutamate metabolism, such as proline, ornithine, and citrulline.

A significant question is the extent to which transamination in the mucosa reduces transfer of various loads of glutamate and glutamine to the portal and systemic bloodstreams. The use of perfused intestinal segments by Windmueller and Spaeth (40) showed that small concentrations (6 mM) of glutamine are not only more rapidly absorbed, but a larger proportion (34%) can be transferred to the portal blood than for glutamate (2%). When the intraluminal concentration was raised to 45 mM, the output of glutamine rose to 70%, but glutamate transfer remained negligible. Thus, deamidation is rate limiting for glutamine metabolism by the gut wall. However, large doses of glutamic acid force-fed to rats do, in fact, raise both portal and systemic plasma levels, as well as elevating alanine and glutamine blood levels (34).

EXCHANGE OF GLUTAMATE AND GLUTAMINE BETWEEN ORGANS

The liver is the main or exclusive site of oxidation of seven of the essential amino acids, the branched-chain amino acids being oxidized mostly in muscle and kidney (10). On the other hand, the metabolism of the nonessential amino acids, including glutamate, is widespread in the tissues of the body. The liver is subjected to an extensive increase in amino acid supply through the portal vein, often leading to a 10-fold increment in the levels of some amino acids in the portal blood (24). The liver is nevertheless able to monitor these large loads. Thus, Elwyn (10) reports a study on dogs in which cannulas were implanted in the portal vein and hepatic artery, both providing blood for the liver, and in the hepatic vein, removing blood from the liver. In this way amino acid exchange and urea output by the liver could be monitored over a 12-hr period after feeding a large meal of meat (Fig. 1). It was found that 57% of the absorbed amino acid load was converted to urea as it passed through the liver and 6% to plasma proteins, whereas only 23% of the absorbed amino acids entered the general circulation as free amino acids; the remaining 14% not accounted for was presumed to be temporarily retained in the liver as hepatic protein (enzymes). These findings indicate that the systemic circulation is protected against excessive changes in free amino acid concentrations by temporary adaptive responses within the liver. To be physiologically useful, the hepatic response would need to be sensitive to the needs of the body, and, since the liver is the major site of

degradation of many essential amino acids, it has to discriminate between suboptimal and superoptimal amounts; and this has indeed been shown to be the case. For example, Harper (18) fed young rats different levels of dietary casein from insufficient up to quantities exceeding their needs for growth. Threonine-serine dehydratase activity in the liver remained low until the casein content of the diet reached 20%, which is optimal for growth of the rat; at intakes above 20%, the activity of this enzyme rose sharply. In contrast, the activity of two transaminases handling glutamic acid rose progressively with dietary protein intake.

Elwyn's study (10) provides us with a balance sheet of the exchange of glutamic acid, glutamine, and alanine across the gut and liver, both in the fed and fasting dog. Table 1 shows that the fed dog transferred more of the intake of total glutamic acid (glutamate plus glutamine in meat protein) into the portal vein as glutamine than as glutamic acid, in agreement with the studies of Windmueller and Spaeth (40) cited earlier; however, a large output of glutathione into the red cells could account for much of the missing glutamic acid. There was also a considerable output of alanine from the gut. In contrast, the liver removed glutamic acid, glutamine, and alanine from the portal blood, so that the net result of passage of blood through the splanchnic area was a small reduction in the levels of all three amino acids. During the postabsorptive period (not shown in Table 1), more glutamine and alanine were extracted from the blood as it passed across the splanchnic area.

TABLE 1. *Exchanges of glutamic acid, glutamine, and alanine across the viscera and limb muscles*

Species	Total exchange during period		
	Glutamic acid	Glutamine	Alanine
Fed dog (mmoles/12 hr)[a]			
Absorbed from gut lumen	—— 160 ——		100
Gut output	+10	+50	+230
Liver output	−15	−70	−260
Total splanchnic output	−5	−20	−30
Fed sheep (mmoles/hr)[b]			
Portal viscera output	−0.2	−1.5	+2.3
Liver output	+1.1	−2.1	−3.2
Total splanchnic output	+0.9	+3.6	−0.9
Hind-quarters output	−11	+13	+14
Fasted human (μmoles/min)[c]			
Total splanchnic output	+48	−59	−60
Leg output	−24	+50	+26

[a] Computed from Elwyn (10). "Glutamic acid" intake from meat protein (160 mmoles) is probably 50% glutamine. Note that glutathione output was 80 mmoles from the gut and 35 mmoles from the liver.

[b] From Bergman and Heitmann (4). Note that the hind-quarters output is given as μmoles/liter, estimated blood flow being unavailable.

[c] From Felig et al. (13), with the figure for alanine output from muscle taken from Felig et al. (12).

These findings are amplified by studies on sheep (4) and man (13), in which plasma was measured instead of whole blood. This is unfortunate, since Elwyn et al. (11) reported that glutamate is present in higher concentration in the red cells and that glutamate in red cells and plasma behave differently during transit across the splanchnic area. In the case of fed sheep (Table 1), Bergman and Heitmann (4) have demonstrated by cannulation of the appropriate vessels that glutamine and a small amount of glutamate are removed from the plasma as it perfuses the gut and other portal viscera; the liver removes further glutamine, but adds a significant amount of glutamate to the plasma. On the other hand, the portal viscera put out alanine, whereas the liver takes it up. This general picture of the exchange across the splanchnic area, including the liver (uptake of glutamine and alanine, with a smaller output of glutamic acid), is confirmed by studies on the plasma of human subjects (13) (Table 1).

These patterns of amino acid metabolism in the viscera are dependent on exchanges of the same amino acids in the peripheral tissues, notably muscle. Muscle represents the major depot within the body of free amino acids (24) and is also the largest single component of body protein. Changes in muscle amino acid flux can thus have a considerable effect on their concentrations in the blood and their availability to other organs. In the fasting human, it has been shown that muscle releases large amounts of alanine (35) and glutamine (13), and, as shown above, these two amino acids are removed by the viscera. This is most clearly seen in the fasting subject (Table 1), who demonstrates a net uptake of glutamic acid and a release of glutamine and alanine as blood passes through the leg muscles. A similar picture is seen for sheep (Table 1). In the case of both humans (13) and sheep (4), the output of glutamine and alanine is greater in the fasting than in the fed state, thus providing a source of carbon for gluconeogenesis during fasting. Details of the reactions involved in the formation of glutamine and alanine are shown in Fig. 3. It will be noted that the state of protein synthesis or breakdown can affect the availability of the free amino acid pool within muscle, and that excretion of the nonreutilizable amino acid 3-methylhistidine allows the investigator to have an independent measure of the contribution of the breakdown of muscle protein to this pool (8).

In summary, Fig. 4 shows the overall picture of glutamic acid, glutamine, and alanine in relation to their uptake and release by the visceral and peripheral organs. The net output of amino acids by the arm or leg muscles of fasting human subjects has been used to compute total muscle protein breakdown, assessed at 75 g per day in the fasting subject (35). We (8) have used the urinary output of the nonreutilized amino acid 3-methylhistidine as a specific index of myofibrillar muscle protein breakdown and obtain a comparable figure (50 g daily).

MAGNITUDE OF GLUTAMATE POOLS AND FLUXES

Beginning with the preceding information, we can assemble a composite picture of the flux of glutamic acid and glutamine in the body. Figure 5 reconstructs amino

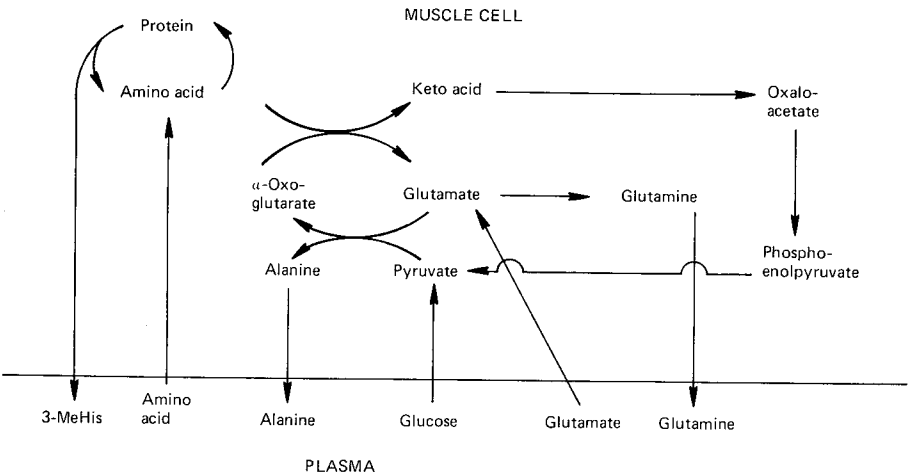

FIG. 3. Interactions of certain amino acids between plasma and muscle. Note that the identification (15) of the enzyme phosphoenolpyruvate carboxykinase in muscle allows the utilization of keto-acids for synthesis of pyruvate as an acceptor of amino groups.

acid turnover in a 70-kg man. The customary protein intake in Western countries is 100 g daily, and some 70 g protein is secreted or shed into the lumen of the gut. In consequence, about 160 g protein are absorbed. The daily turnover of body protein is computed to be about 300 g. The difference between intake of 100 g and turnover of 300 g thus represents the recycling of amino acids and implies a dynamic state for the free amino acid pool. The free amino pools in the tissues constitute at least 70 g, of which the greater part consists of four nonessential amino acids, namely, alanine, glutamic acid, glutamine, and glycine (24).

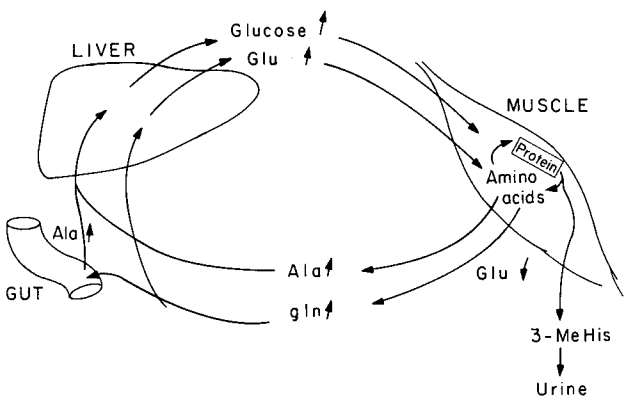

FIG. 4. Interchange of glutamic acid, glutamine, alanine, and glucose between muscle, intestinal mucosa, and liver.

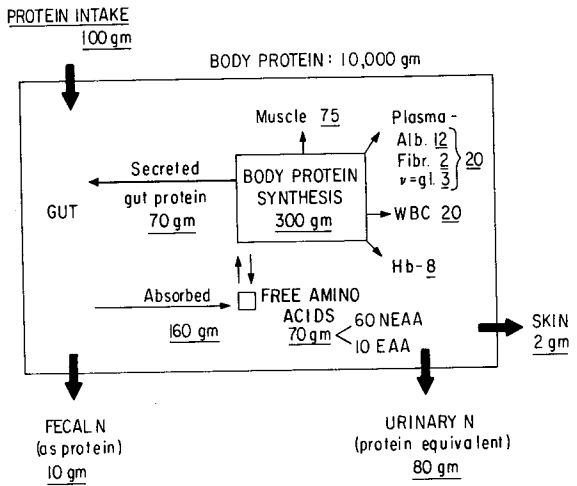

FIG. 5. Diagram illustrating the daily flux of amino acids in the body of a 70-kg man. (From Munro, ref. 26.)

This general picture can be made specific for glutamic and aspartic acids (Table 2). Using data for *total* dicarboxylic acids (glutamic acid and glutamine and aspartic acid and asparagine), estimates of some aspects of glutamic acid and aspartic acid flux can be computed. The most striking features are the large amounts of glutamic and aspartic acids released from body protein in the course of turnover and the very small amounts of these dicarboxylic amino acids in the plasma. If the plasma is to act as an effective channel for transport, the turnover of these plasma amino acids must be very rapid, and, indeed, Elwyn et al. (11) have estimated their plasma half-life to be less than 1 min.

TABLE 2. *Daily flux of glutamic and aspartic acids in a 70-kg man*[a]

Source of amino acids	Total amino acids (g)	Glutamic acid (g)	Aspartic acid (g)
Dietary protein	101	20	8
Endogenous gut protein	70	8	6
Body protein			
Total	10,000	1,600	900
Daily turnover	300	48	27
Free amino acids			
Plasma	—	0.02	0.004
Muscle	86	20	4

[a] Flux of total amino acids taken from Munro (26). Flux of glutamic and aspartic acids (including their amides) based on their abundance in the proteins of the average diet (7) and in tissue proteins (27). Pools of plasma and muscle free glutamic and aspartic acid are computed from data of Bergstrom et al. (5).

These data for man can be viewed in relation to other mammalian species. Elsewhere, an account of the influence of the size of species on intensity of metabolism has been given (22). The analysis of various parameters shows that the intensity of metabolism is about five times greater in the rat than in man. Table 3 illustrates this by showing the turnover of plasma albumin in a number of mammals. Whereas the renewal rate for plasma albumin is 59% in the mouse, it is only 4% in man, species of intervening size having intermediate rates of turnover. The amount of RNA per cell in the liver (the site of albumin synthesis) can be correlated with this decline in turnover rate. However, Table 3 shows that the levels of essential and nonessential amino acids in liver and muscle, and the levels of glutamic and aspartic acids and glutamine in plasma, show no consistent relationship to the size of a species. Thus, when comparisons are made between glutamate metabolism in man and small species such as the rat, these differences in metabolic intensity should be recognized.

HORMONES AND GLUTAMATE METABOLISM

Hormones affect the levels of free glutamic acid and glutamine through changes in the entry and exit of these amino acids between body compartments. For example, the administration of corticosteroids to rats (6) has been shown to increase the levels of glutamic and aspartic acids and of alanine in muscle, plasma, and liver. This is probably mediated by an increase in muscle protein breakdown resulting from corticosteroid administration, as evidenced by an increased output of 3-methylhistidine from the breakdown of muscle protein (28). Plasma glutamate is also elevated by hyperthyroidism in man, but administration of an oral load of glutamate is tolerated normally (3). Urinary excretion of glutamate is also increased in the hyperthyroid state.

RESPONSES TO CHANGES IN DIET

Enzymes of glutamic acid metabolism respond to changes in protein intake, due to the involvement of glutamate as a nitrogen donor in many reactions, including urea synthesis. In a recent study, McGivan et al. (21) have shown that transport of glutamate across the mitochondrial membrane can be rate limiting for urea synthesis in the liver and that this intracellular transport mechanism is enhanced in carrier capacity by raising the protein intake. In addition, liver transaminases involving glutamate undergo increased activity as the intake of dietary protein is increased (18).

Studies of the toxicity levels of dietary free amino acids have been reviewed by Harper (19). Based on a variety of factors, but mainly on rate of growth of young rats, methionine was most toxic (above 1.5% of the diet) and glutamic acid least toxic (7% of diet). In a study on young rats force-fed a meal containing 5% glutamic acid, Peng et al. (33) observed a doubling of plasma glutamate and a 60% increase in plasma alanine, but no change in the levels of either amino acid in brain. A few

TABLE 3. *Effect of size of species of mammal on body protein turnover, liver RNA content, and free amino acid pools*[a]

Species	Body weight (kg)	Albumin synthesis (fractional rate/day (%)	Liver RNA/DNA	Liver amino acids[b]		Muscle amino acids[b]		Plasma amino acids[b]				
				Essential	Nonessential	Essential	Nonessential	Essential	Nonessential	Aspartic acid	Glutamic acid	Glutamine
				(μmoles/g)		(μmoles/g)		(μmoles/ml)				
Mouse	0.03	59	4.5	1.2	6.6	1.1	5.5	0.5	0.8	0.01	0.04	0.49
Rat	0.2	28	3.1	0.8	4.2	0.8	4.0	0.7	1.1	0.02	0.07	0.62
Rabbit	2	12	2.4	1.4	3.9	0.6	4.0	0.5	1.6	0.02	0.10	0.59
Dog	30	9	1.7	0.8	2.6	0.7	2.9	0.6	0.8	0.01	0.04	—
Man	70	4	—	—	—	1.4	8.0	0.7	0.8	0.01	0.05	0.51

[a] Data from Munro (22), with data for man from Bergstrom et al. (5).
[b] Essential amino acids = sum of isoleucine, leucine, phenylalanine, and valine; nonessential amino acids = sum of alanine, aspartic acid, glutamic acid, glycine, and serine.

human studies also suggest a high tolerance for glutamic acid. In human studies of the amino acid needs of boys, Nakagawa et al. (29) observed no toxic effects when 12.75 g free glutamic acid were fed daily. This picture of the efficient metabolic removal of orally administered excess glutamate in humans is reflected in the finding that free glutamic acid levels in the plasma are the least affected by meal-related diurnal rhythms (42) and by infusion of glutamate into the intestine (2). A study (32) in which a large meal of protein was given to human subjects also failed to raise plasma glutamate, but did cause an increase in glutamine concentration. This may represent the more extensive absorption of glutamine than of glutamic acid across the gut mucosa noted earlier.

CONCLUSION

The metabolism of glutamic acid and glutamine involves cooperation between tissues. The daily intakes of these amino acids from the diet are large; the body pools are also extensive; nonetheless, the total amounts present in the plasma are small. Thus, the regulation of the plasma concentrations of glutamic acid and glutamine is an important aspect of their metabolism. This is achieved by restricting the passage of these amino acids across the intestinal mucosa, and by efficient removal by organs such as the intestine. It is, however, still too early to assemble a quantitative picture of the overall metabolism of these amino acids in the body because of the need for more quantitative information on their transport and metabolism at the subcellular level.

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