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The effect of carbohydrate and protein administration on amino acids in the pancreas, brain, intestine, and plasma of the rat

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We measured the concentration of the large neutral amino acids (LNAA) in the plasma, pancreas, brain and intestine of rats that were given protein or carbohydrate intragastrically. In the brain it is well known that competition for entry occurs at the level of the blood-brain barrier between the various LNAA and that brain levels of LNAA are predicted not by their plasma level but by the ratio of the plasma level of each of the LNAA to the sum of the other LNAA (the plasma amino acid ratio). We have found that carbohydrate ingestion increased brain histidine as well as brain tryptophan. Levels of amino acids in the pancreas, like those in the brain, were found to be correlated with their plasma ratios and not with the simple plasma levels. Thus, for example, after carbohydrate the level of the aromatic amino acids increased and the level of the branched chain amino acids decreased in both brain and pancreas. These changes were similar to those that occurred in the various plasma LNAA ratios. As expected, no such relationship was seen in the intestine. These results indicate that the system transporting LNAA into the pancreas is similar to that in the brain and different from the transport system in other tissues. Whether the competition is taking place at the level of the capillaries, as in the brain, or at the level of the cell membrane remains to be determined as does the functional significance of these findings. (J. Nutr. Biochem. 6:564–569, 1995.)

Keywords: tryptophan; large neutral amino acids; brain; pancreas; transport

Introduction

Amino acids are taken up into tissues by transport mechanisms specific for acidic, basic, and neutral amino acids.[1–3] Amino acids of the same class do not usually compete for transport across the cell membrane because competition can only take place when the K_m of the carrier is of the same order of magnitude as the concentration of the amino acids in the plasma.[4] The K_m at most cell membranes is much greater than the plasma concentration of the amino acids[5] except at the blood-brain barrier where a unique high affinity transport system (i.e., low K_m) of the large neutral amino acids (LNAA) leads to a carrier that is close to saturation.[5] Therefore, at the blood brain barrier, the LNAA must compete for uptake.[2] The amount of amino acid that can be transported across the blood-brain barrier depends not only on the concentration of that particular amino acid but also on the concentration of the competing amino acids. Strong correlations have been found between the plasma ratio of each LNAA to the sum of the competing amino acids and its brain level.[6] Since some of the large LNAA are precursors to neurotransmitters, and the brain level of these precursors can in some circumstances influence the synthesis of their product neurotransmitters, competition at the blood-brain barrier may play a role in regulating neurotransmitter synthesis.[7]

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Physiological situations such as diabetes,[8] stress,[9] and dietary intake[6,10] can influence plasma amino acid levels. The dietary macronutrients, protein and carbohydrate, influence the concentration of plasma LNAA differently. Ingestion of protein increases the concentration of all amino acids in the plasma. In contrast, carbohydrate tends to lower plasma amino acid levels, particularly the branched-chain amino acids that are taken up into muscle due to the release of insulin.[11] In most tissues, for example the liver, where competition between the LNAA does not take place, increases or decreases in plasma levels result in similar changes in tissue amino acid levels.[12]

The effects of the macronutrients on plasma and tissue tryptophan levels differ from those of the other amino acids. This is because tryptophan is the least abundant amino acid in protein. After protein ingestion, the increase in plasma tryptophan is relatively small in comparison with the other LNAA. Therefore, the ratio of tryptophan to the sum of the competing amino acids declines, and this can result in a decrease in brain tryptophan.[13,14] After carbohydrate intake, plasma tryptophan either remains stable[13] or increases.[15] The concentration of the competitors declines due to the effect of insulin. As a result, the plasma ratio of tryptophan to the sum of the competing amino acids is elevated. The tryptophan content of muscle, intestine, and liver remains unchanged after carbohydrate intake,[15] but brain tryptophan is increased.

Until recently the brain was thought to be the only tissue sensitive to competition between plasma amino acids. However, in a recent paper,[14] we showed that tryptophan levels in the pancreas were lowered by protein administration and elevated by carbohydrate. Furthermore, intraperitoneal administration of valine, a LNAA that competes with tryptophan for uptake at the blood-brain barrier, was shown to lower pancreatic tryptophan. These data raise the possibility that competition between amino acids for entry into the pancreas may play some role in regulating the level of amino acids in the pancreas. In this paper we have examined the effect of protein and carbohydrate administration on amino acids in the pancreas, brain, intestine, and plasma. Our objectives were to determine if the effects previously reported were specific to tryptophan or were common to the group of large LNAA and to compare the effects on the pancreas with those on the brain and intestine.

Methods and materials

Male Sprague–Dawley rats obtained from Charles River Canada, Inc. (St. Constant, Québec, Canada), weighing between 190 and 210 g, were maintained on a 12–12 hr light–dark cycle (lights on at 6:00 a.m.) for a period of 1 week before the experiment. During the pretrial period, the animals were maintained on standard Purina rat chow. On the experimental day, animals were randomly assigned to groups of eight. The rats were fasted overnight for a 15 hr period, and treatments were administered 3 hr after light onset, at 9:00 a.m. All treatments were administered intragastrically to avoid the effects of the sensory component of the foods. The protein treatment consisted of 4 mL of a 25% wt/vol solution of albumin. The carbohydrate treatment was 4 mL of a 50% wt/vol glucose solution. An identical volume of water acted as the control in the fasted animals. Since most meals generally contain twice the amount of carbohydrate as protein, we followed these proportions and administered twice as much carbohydrate as protein. The treatments were identical as those used in a previous study[14] and were selected because they represented pure forms of each macronutrient. Animals were decapitated 2.0 hr after intubation, at which time trunk blood was collected. Brains and pancreases were removed and frozen immediately at −70°C. Intestines were removed and rinsed inside and outside with saline before freezing. The animal experiments were approved by the McGill University Animal Care Committee, which operates under the guidelines of the Canadian Council on Animal Care.

For brain, intestine, and pancreas, a 25% homogenate was made using distilled water and a Polytron homogenizer. A portion of the homogenate was aliquoted and frozen for subsequent analysis of tryptophan. To measure the other amino acids, 1 mL of the homogenate was mixed in a test tube with 50 mg of sulphosalicylic acid, placed in a cold room at 4°C for 1 hr, and then centrifuged at 2,000*g* for 10 min. Five hundred microliters of the supernatant was then mixed with 350 μL of 0.3 N LiOH. This solution was then filtered through a 0.2 μm membrane and injected into an LKB Alpha Plus amino acid analyzer using a high resolution column. For plasma, a similar procedure was used, except a 2.5:1.0 ratio of supernatant to 0.3 M LiOH was used. Tryptophan in the tissues and blood was analyzed by the fluorometric method of Denckla and Dewey.[16]

When calculating plasma ratios of a particular amino acid to the sum of the other LNAA, we used levels of tryptophan, phenylalanine, tyrosine, histidine, isoleucine, leucine, valine, and methionine in the calculations. Although other researchers have not used histidine and methionine in similar calculations, they are certainly transported into brain by the LNAA system.[1,2]

Statistical analysis of differences between the three groups was performed using a one-way analysis of variance. Significant differences between means were determined by Tukey's test. Relationships between amino acid ratios and tissue amino acid content were analyzed using Pearson product-moment correlations.

Results

The effects of protein and carbohydrate on the large neutral amino acids in plasma, brain, intestine, and pancreas are shown in *Table 1*. In addition, the plasma amino acid ratios (plasma concentration of the individual amino acid divided by the sum of the plasma concentration of the other large neutral amino acids) are given. All the amino acids in plasma were lowered by carbohydrate treatment except for tryptophan and methionine which were unaffected. Protein elevated all the plasma amino acids with the exception of tryptophan and histidine. Plasma ratios of tryptophan:LNAA, phenylalanine:LNAA, histidine:LNAA, and methionine:LNAA were elevated by carbohydrate but the plasma leucine and valine ratios were lowered. No effect of protein on the plasma ratios was demonstrated, except for valine, which was significantly elevated.

Brain levels of the individual amino acids corresponded closely with the plasma ratios. Thus, carbohydrate significantly elevated tryptophan, phenylalanine, and histidine in the brain. The effect on brain tryptophan and phenylalanine agrees with previously reported data, while to our knowledge this effect had not previously been observed for brain histidine. The branched chain amino acids isoleucine, valine, and leucine were lowered by the carbohydrate treatment. In contrast, protein had no effect on any of the brain amino acids measured. Although this result was consistent with the lack of change on the plasma amino acid ratios

Table 1 Effect of carbohydrate and protein on large neutral amino acids in the plasma, brain, pancreas, and intestine

Amino acids	Fasted	Carbohydrate	Protein
Tryptophan			
Plasma	131 ± 23	137 ± 27	147 ± 23
Plasma ratio	0.147 ± 0.024	0.313 ± 0.069*	0.127 ± 0.023
Brain	30 ± 5	40 ± 6*	29 ± 4
Pancreas	135 ± 25	169 ± 25*	97 ± 14*
Intestine	303 ± 80	253 ± 80	334 ± 155
Phenylalanine			
Plasma	74 ± 6	64 ± 5*	91 ± 9*
Plasma ratio	0.079 ± 0.006	0.128 ± 0.015*	0.074 ± 0.003
Brain	74 ± 8	108 ± 19*	78 ± 11
Pancreas	152 ± 40	286 ± 75*	151 ± 74
Intestine	428 ± 156	441 ± 100	606 ± 148†
Tyrosine			
Plasma	118 ± 14	76 ± 6*	157 ± 27*
Plasma ratio	0.132 ± 0.018	0.152 ± 0.011	0.135 ± 0.017
Brain	106 ± 9	118 ± 13	103 ± 17
Pancreas	353 ± 60	405 ± 75	341 ± 74
Intestine	461 ± 141	468 ± 108	649 ± 152*
Isoleucine			
Plasma	129 ± 12	38 ± 4*	151 ± 10*
Plasma ratio	0.116 ± 0.034	0.119 ± 0.036	0.107 ± 0.036
Brain	53 ± 6	41 ± 7*	56 ± 10
Pancreas	131 ± 40	89 ± 25*	92 ± 15*
Intestine	332 ± 94	291 ± 63	542 ± 107†
Leucine			
Plasma	187 ± 17	65 ± 7*	238 ± 16*
Plasma ratio	0.225 ± 0.017	0.132 ± 0.025*	0.223 ± 0.009
Brain	107 ± 13	83 ± 11*	111 ± 8
Pancreas	288 ± 79	223 ± 56	234 ± 39
Intestine	681 ± 223	679 ± 162	1,020 ± 231†
Valine			
Plasma	226 ± 24	79 ± 7*	322 ± 27*
Plasma ratio	0.286 ± 0.030	0.162 ± 0.029*	0.325 ± 0.018*
Brain	88 ± 10	68 ± 10*	94 ± 15
Pancreas	264 ± 85	206 ± 28	264 ± 34
Intestine	500 ± 152	454 ± 109	820 ± 158†
Histidine			
Plasma	73 ± 6	54 ± 11*	83 ± 10
Plasma ratio	0.077 ± 0.008	0.110 ± 0.326*	0.069 ± 0.010
Brain	65 ± 7	74 ± 5*	64 ± 6
Pancreas	154 ± 47	218 ± 63*	124 ± 19
Intestine	146 ± 39	148 ± 22	212 ± 34*
Methionine			
Plasma	81 ± 9	72 ± 4	125 ± 21*
Plasma ratio	0.087 ± 0.011	0.145 ± 0.021*	0.105 ± 0.013
Brain	64 ± 17	81 ± 15	75 ± 17
Pancreas	148 ± 23	199 ± 36*	190 ± 33*
Intestine	372 ± 98	353 ± 85	500 ± 129

The experiment was carried out as described in the Methods and materials section. Results are the mean of 8 ± SD in nmol/mL. Plasma amino acid ratio refers to the ratio of the plasma concentration of an individual amino acid to the sum of the plasma concentrations of the other large neutral amino acids which include tryptophan, phenylalanine, tyrosine, histidine, isoleucine, leucine, valine, and methionine minus the individual amino acid.
*$P < 0.05$ compared with the fasting value.
†$P < 0.01$.

(used as an index of LNAA availability to the brain), it was in contrast to our previous results which showed a decrease in brain tryptophan after protein.[14]

The effect of the macronutrients on pancreatic amino acids paralleled the observed effects on the brain as carbohydrate increased pancreatic tryptophan, phenylalanine, and histidine while protein significantly lowered pancreatic tryptophan and isoleucine. Methionine increased after both protein and carbohydrate treatments. In the intestine, carbohydrate had no effect on any of the large neutral amino acids. However, protein raised the levels of almost all the amino acids including phenylalanine, tyrosine, isoleucine, leucine, valine, and histidine. Tryptophan and methionine were increased but the differences from fasted animals were not significant.

Table 2 shows the effect of protein and carbohydrate on acidic and basic amino acids which do not compete for the same carrier as the LNAA for transport across the blood-brain barrier. In general carbohydrate lowered plasma levels of these amino acids and protein increased plasma levels, except for alanine, the gluconeogenic amino acid, which was increased by both treatments. Brain levels of threonine, serine, alanine, ornithine, lysine, and arginine were unaffected by either dietary treatment. Alanine was the only pancreatic amino acid in this group that was affected by dietary treatment because both carbohydrate and protein increased its concentration. Alanine was also increased in the intestine by both dietary manipulations while serine in the intestine was only increased by protein. None of the other

Table 2 Effect of carbohydrate and protein on acidic and basic amino acids in the plasma, brain, pancreas and intestine

Amino acids	Fasted	Carbohydrate	Protein
Threonine			
Plasma	353 ± 51	212 ± 22*	457 ± 64*
Brain	597 ± 85	663 ± 95	621 ± 65
Pancreas	1,110 ± 337	1,170 ± 319	988 ± 172
Intestine	770 ± 263	807 ± 167	120 ± 175*
Serine			
Plasma	313 ± 21	212 ± 24*	391 ± 37*
Brain	765 ± 100	763 ± 98	784 ± 39
Pancreas	1,100 ± 117	1,090 ± 214	969 ± 154
Intestine	1,150 ± 346	1,180 ± 235	1,590 ± 318*
Alanine			
Plasma	388 ± 26	498 ± 47*	529 ± 65*
Brain	536 ± 43	550 ± 69	513 ± 30
Pancreas	869 ± 274	2,370 ± 507*	1,460 ± 448*
Intestine	2,260 ± 562	2,800 ± 353†	2,990 ± 278†
Ornithine			
Plasma	88 ± 21	54 ± 10*	105 ± 18
Brain	42 ± 15	42 ± 8	42 ± 13
Pancreas	177 ± 30	174 ± 37	149 ± 19
Intestine	149 ± 39	145 ± 38	157 ± 41
Lysine			
Plasma	423 ± 99	290 ± 34*	537 ± 113*
Brain	386 ± 52	393 ± 37	386 ± 56
Pancreas	637 ± 158	654 ± 161	556 ± 105
Intestine	636 ± 209	701 ± 142	798 ± 214
Arginine			
Plasma	166 ± 21	120 ± 10*	227 ± 57*
Brain	172 ± 15	175 ± 23	185 ± 32
Pancreas	183 ± 29	190 ± 38	169 ± 25
Intestine	763 ± 416	729 ± 280	986 ± 439

The experiment was carried out as described in the Methods and materials section. Results are the mean of 8 ± SD in nmol/mL. Plasma amino acid ratio refers to the ratio of the plasma concentration of an individual amino acid to the sum of the plasma concentrations of the other large neutral amino acids which include tryptophan, phenylalanine, tyrosine, histidine, isoleucine, leucine, valine, and methionine minus the individual amino acid.
*$P < 0.05$ compared with the fasting value.
†$P < 0.01$.

amino acid concentrations in the intestine were affected by protein or carbohydrate treatment.

Table 3 shows the correlation coefficients between the plasma amino acids and the brain, pancreatic, and intestinal concentration of each amino acid as well as the correlation coefficient between the plasma ratio and the tissue concentrations. Only levels of plasma isoleucine and leucine were found to be significantly correlated with brain levels. In contrast, significant correlations were found for seven out of the eight LNAA when the relationship between the plasma ratios and brain levels were compared, methionine being the exception. The pancreas exhibited a similar response as the brain with few associations between plasma and pancreatic level but many highly significant correlations between the plasma amino acid ratios and the pancreatic amino acid concentrations. For example, only plasma phenylalanine and methionine were found to be significantly negatively correlated with the pancreatic concentrations of these amino acids, but the plasma amino acid ratios were highly correlated for all the LNAA except histidine and leucine, which showed correlations that were positive but not significant. For the intestine, all correlations were low and only that for valine reached significance.

Table 3 Correlations between plasma amino acids, plasma amino acid ratios, and tissue amino acid concentrations

Amino acid	Brain	Pancreas	Intestine
Tryptophan			
Plasma	0.09	0.16	0.19
Plasma ratio	0.65*	0.69*	−0.09
Phenylalanine			
Plasma	−0.42	−0.59†	0.40
Plasma ratio	0.62*	0.74*	0.09
Tyrosine			
Plasma	−0.24	−0.32	0.53†
Plasma ratio	0.70*	0.45†	−0.02
Isoleucine			
Plasma	0.69*	0.21	0.58†
Plasma ratio	0.57*	0.41†	0.34
Leucine			
Plasma	0.73*	0.22	0.44
Plasma ratio	0.69*	0.38	0.05
Valine			
Plasma	−0.12	0.46	0.65*
Plasma ratio	0.66*	0.54*	0.47†
Histidine			
Plasma	−0.07	0.10	0.27
Plasma ratio	0.55*	0.26	−0.14
Methionine			
Plasma	−0.45	−0.68*	0.43
Plasma ratio	0.30	0.49†	−0.24

Pearson product-moment correlations were calculated between the plasma ratio of each amino acid to the sum of the other LNAA and the tissue concentration of the same amino acid. For all correlations 24 pairs of values (eight from each of the experimental groups) were used. Plasma amino acid ratio refers to the ratio of the plasma concentration of an individual amino acid to the sum of the plasma concentrations of the other large neutral amino acids which include tryptophan, phenylalanine, tyrosine, histidine, isoleucine, leucine, valine, and methionine minus the individual amino acid.
*$P < 0.001$; †$P < 0.01$.

Discussion

The results of this study confirm and extend our previous findings on the differential effects of intragastric protein and carbohydrate administration on amino acid levels in different tissues. In common with many other researchers, we found that carbohydrate significantly lowered the plasma levels of almost all amino acids, resulting in an increase in the plasma ratio of tryptophan:LNAA as well as phenylalanine:LNAA, histidine:LNAA, and methionine:LNAA (*Table 1*). The increased plasma ratio was reflected by increases in the brain concentration of these same amino acids, while the decreases shown in the plasma ratios of both leucine:LNAA and valine:LNAA resulted in a decline in brain levels (*Table 1*).

The effect of carbohydrate on the plasma ratio of histidine:LNAA and the subsequent rise in brain histidine levels is worth noting. This basic amino acid is, at physiological pH, primarily neutral and thus able to compete for transporter with the LNAA.[1] We found a significant correlation between the plasma histidine:LNAA ratio and brain histidine, supporting this hypothesis (*Table 3*). In one study, rat brain histidine was increased after a protein meal.[13] However, after chronic protein deficiency, rats exhibit elevated brain histidine levels,[17] and as casein is increased in the diet brain histidine declines.[18] Thus, chronic effects on histidine may differ from acute dietary effects. In humans, we found increases in the plasma histidine:LNAA ratio after carbohydrate, which were of the same order of magnitude as those changes observed in the plasma tryptophan:LNAA ratio.[19] Since the rate-limiting enzyme in histamine synthesis, histidine decarboxylase, is normally unsaturated with histidine,[20] protein and carbohydrate meals are as likely to influence brain histamine as serotonin. While little is known about the physiological function of brain histamine, possible dietary effects on brain histamine should be taken into account in studies on the behavioral effects of food. For example, it has been proposed that food intake can be predicted as a function of brain histidine levels.[21]

The effects of protein administration were more equivocal than those of carbohydrate. Although protein increased the plasma amino acid concentrations of all amino acids except for tryptophan and ornithine, only the plasma ratio of valine to the sum of the LNAA was increased significantly. No significant decline in the plasma tryptophan:LNAA ratio was observed. Correspondingly, brain levels were unaffected, in keeping with the highly significant correlation between the plasma tryptophan:LNAA ratio and brain tryptophan (*Table 3*). Generally, the present data agree with those of Voog and Eriksson[22] who found significant correlations between the plasma amino acid ratios and brain levels of the LNAAs after rats ingested diets of varying protein content. However, this group also found significant correlations between all plasma amino acids and brain levels (with the exception of tryptophan and isoleucine) while we only found correlations for plasma leucine and isoleucine.

Fernstrom and Faller[6] did not find any change in either the plasma tryptophan:LNAA ratio or in brain tryptophan after a 40% protein diet, but their results and our own

present results disagree with those of Glaeser et al.[13] who found a significant decrease in brain tryptophan after protein and also our own previous results demonstrating that the administration of pure protein decreased brain tryptophan.[14] The discrepancies in the findings are not surprising. Upon close examination of the literature, there is no consistency in the reports on the effect of macronutrients on the plasma tryptophan:LNAA ratio and brain tryptophan. For example carbohydrate can increase plasma tryptophan[10,15] or have no effect.[8,13] While carbohydrate usually increases brain levels of tryptophan,[8,10] there are also cases where no effect is observed[13] (Teff and Young, unpublished data). Therefore, it is not surprising that in a previous study we found a significant decrease in brain tryptophan after protein,[14] but in the present study we only found a nonsignificant trend in that direction.

The regulation of plasma and brain amino acid levels involves a number of factors including the pretreatment diet, the levels of various hormones, the net rate of protein synthesis, and the level of the enzymes that degrade amino acids, all of which may combine in complex ways in physiological circumstances. Fasting, for example, increases brain tryptophan,[23] and could create a ceiling effect whereby maximal levels of brain tryptophan, once reached, cannot be elevated further by carbohydrate ingestion.[24] Stress has also been found to alter brain levels of tryptophan.[25] Originally this effect was thought to be due to an increase in nonalbumin bound tryptophan, but it has since been found that restraint stress increases the brain levels of other LNAA as well. The authors postulated that the kinetics of transport across the blood-brain barrier are altered by stress.[9] Since even mild psychological stress, such as the removal of group-housed rats from their cages, has been shown to alter nonalbumin bound tryptophan,[26] it is possible that subtle differences in caging and handling may alter plasma and brain levels of amino acids. Finally, an important determinant of tryptophan may be individual variation as illustrated in a study on the effect of tryptophan administration on tryptophan concentrations in rat cerebrospinal fluid where 7 to 10 fold differences in response were seen in different animals.[27]

In the intestine, protein increased levels of all the LNAA increased (*Table 1*), in most cases significantly, due to the increased availability of the amino acids. After carbohydrate, although the plasma levels of most of the LNAA declined significantly, the levels in the intestine were unchanged, except for that of alanine, the primary gluconeogenic amino acid,[28] which increased. This suggests that the LNAA in the intestine may be relatively insensitive to changes in plasma amino acids. The increase in LNAA in the intestine after protein may have been due, in whole or in part, to direct absorption of the amino acids from the gut lumen. Whatever the explanation, there is no evidence that competition occurs between the LNAA for entry into the intestine, either from these data or from the correlations between the plasma amino acid ratios and intestinal amino acid competitions (*Table 3*).

The effect of carbohydrate on brain and pancreas (*Table 1*) were similar, with increased levels of the aromatic amino acids, and lowered levels of the branched chain amino acids with the exception of methionine and alanine (*Table 2*) which were unaltered in the brain but increased significantly in the pancreas. In general, the observed changes correspond with alterations in the plasma amino acid ratios (*Table 3*). Changes after protein were less marked, but there was a significant decline in pancreatic tryptophan, in agreement with our earlier findings.[14] The important finding in the protein experiment is that pancreatic LNAA did not increase, although increases occurred in LNAA in plasma and intestine (*Table 1*). Although we found no change in the plasma tryptophan:LNAA ratio in blood collected at the time the rats were killed, presumably there was such a change in the blood supplying the pancreas at an earlier time, thus accounting for the decline in tryptophan levels in the pancreas. The similarities in the changes in the amino acids in brain and pancreas, and the correlations between the amino acid ratios and the amino acid concentrations in brain and pancreas (*Table 3*), suggest that the properties of the transport system for the LNAA in pancreas is similar to that in brain.

Only a few studies have examined the effect of diet on pancreatic indoles. However, there does seem to be agreement that carbohydrate can raise serotonin in the pancreas.[14,29] As tryptophan administration can increase serotonin in rat pancreas,[14] the effect of carbohydrate is presumably due to increased pancreatic tryptophan. Bender[30] found that pancreatic tryptophan was elevated in rats deprived of food for 24 hours. Fifteen minutes after glucose administration, a decline in pancreatic tryptophan was observed. This increase in tryptophan in fasted animals was blocked by agents cytotoxic to beta cells in the pancreas,[31] suggesting that it was specific to the insulin-containing cells. The effects we observed on tryptophan in the pancreas with protein and carbohydrate were intermediate in time between the early effects of glucose and the prolonged effects of fasting reported by Bender.[30] Obviously changes in pancreatic tryptophan are complex. Currently there is insufficient information to propose hypotheses about why tryptophan levels in the pancreas change in the way they do and why the pancreas regulates LNAA levels in part by competition between the various LNAA for entry into this tissue. However, our results raise the question of whether altered precursor levels could alter pancreatic monoamine levels and thereby modulate pancreatic function after meal ingestion. Since serotonin has been shown to alter glucose-induced insulin release, carbohydrate ingestion may subsequently increase pancreatic serotonin and ultimately modulate insulin release.[32]

We have shown in this paper that the LNAA in pancreas are regulated by a system similar to that in the brain. To determine whether the systems are identical it would be necessary to do extensive cross-inhibition studies of the type performed in the brain by Oldendorf and Szabo.[1] However, the similarities of the two systems raise the question of where LNAA operates in the pancreas. The blood-brain barrier to the LNAA occurs at the level of the capillaries. The blood-pancreas barrier could occur at the level of the capillaries (although we are not aware of any histological evidence for this) or at the level of the cell membrane.

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