The Stimulus-Secretion Coupling of Amino Acid-induced Insulin Release

INFLUENCE OF A NONMETABOLIZED ANALOG OF LEUCINE ON THE METABOLISM OF GLUTAMINE IN PANCREATIC ISLETS

The nonmetabolized analog of L-leucine, \( \beta(-)-2\)-aminobicyclo[2,2,1]heptane-2-carboxylic acid (BCH). The influence of BCH upon the metabolism of L-glutamine was investigated. In the islets exposed to L-glutamine, BCH decreased the deamidation of glutamine, but stimulated the oxidative deamination of glutamate, increased the rate of generation and islet content of 2-ketoglutarate, and augmented the oxidation of \( ^{14}\text{C}\)glutamine. BCH antagonized the sparing action of L-glutamine upon the oxidation of endogenous fatty acids. The stimulation of insulin release by the association of L-glutamine and BCH was commensurate with the estimated increase in \( \Delta\) consumption and coincided with an increase in the islet NADPH/NADP\(^+\) ratio, net uptake of \( ^{45}\text{Ca} \), and cyclic AMP concentration. It is concluded that insulin release evoked by these amino acids is causally linked to an increased in catabolic fluxes, the secretagogues acting in the islet cells as a fuel (glutamine) or enzyme activator (BCH).

L-Glutamine causes a dose-related enhancement of insulin release evoked, in rat pancreatic islets, by the nonmetabolized analog of leucine, \( \beta(-)-2\)-aminobicyclo[2,2,1]heptane-2-carboxylic acid (BCH). The influence of BCH upon the metabolism of L-glutamine was investigated. In the islets exposed to L-glutamine, BCH decreased the deamidation of glutamine, but stimulated the oxidative deamination of glutamate, increased the rate of generation and islet content of 2-ketoglutarate, and augmented the oxidation of \( ^{14}\text{C}\)glutamine. BCH antagonized the sparing action of L-glutamine upon the oxidation of endogenous fatty acids. The stimulation of insulin release by the association of L-glutamine and BCH was commensurate with the estimated increase in \( \Delta\) consumption and coincided with an increase in the islet NADPH/NADP\(^+\) ratio, net uptake of \( ^{45}\text{Ca} \), and cyclic AMP concentration. It is concluded that insulin release evoked by these amino acids is causally linked to an increased in catabolic fluxes, the secretagogues acting in the islet cells as a fuel (glutamine) or enzyme activator (BCH).

The nonmetabolized analog of L-leucine, \( \beta(-)-2\)-aminobicyclo[2,2,1]heptane-2-carboxylic acid stimulates insulin release from pancreatic islets, even when the latter are deprived of exogenous nutrient (1). The secretory response to BCH is primarily attributable to activation of glutamate dehydrogenase. In a few instances (e.g., measurement of NADPH and NADP\(^+\)), all four experimental conditions (i.e., substrate, L-glutamine alone, \( \beta(-)-BCH \) alone, and both L-glutamine and \( \beta(-)-BCH \) were not tested within the same experiment(s). In such a case, the experimental values were normalized relative to the mean basal value found within the same experiment(s) and converted back to absolute values taking into account the overall mean basal reading derived from all available experiments. For measurement of glutaminase activity (EC 3.5.1.2), groups of 450 islets each were sonicated (twice for 5 s) in 0.3 ml of a bicarbonate-buffered medium (Na\(^+\), 24 K\(^+\), 120 Mg\(^+\), 1 Ca\(^+\), 1 Cl\(^-\), 124 HCO\(_3\)\(^-\), 24 mM) containing bovine albumin (2 mg/ml) and equilibrated against a mixture of CO\(_2\) (5%) and O\(_2\) (95%) (6). Metabolic variables were measured in groups of 15-50 islets each incubated in 40-100 ml of the same bicarbonate-buffered medium. All nucleotides and metabolites were measured in the islets and incubation media treated as a whole. Hence, no distinction was made between the islet content and output of metabolic end products. The net uptake of \( ^{45}\text{Ca} \) was measured by incubating the islets for 90 min in the presence of \( ^{45}\text{Ca} \) and then submitting them to repeated washes in order to remove extracellular radioactivity (12). For measuring the cyclic AMP content of the islets and media, groups of 10 islets each were preincubated for 60 min in media (0.2 ml) containing 2-gucose, 5.6 mM, and then incubated for 60 min in media (0.1 ml) containing the required amino acids and 3-isobutyl-1-methylxanthine (1.0 mM). After incubation, the islets and media were mixed with and sonicated in 0.1 ml of trichloroacetic acid (10%, w/v). The cyclic AMP was then extracted, acetylated, and eventually measured by radioimmunoassay (13).

In each individual experiment, control and experimental values were obtained in close to equal number of distinct batches of islets all derived from the same initial preparation. In a few instances (e.g., measurement of NADPH and NADP\(^+\)), all four experimental conditions (i.e., substrate, L-glutamine alone, \( \beta(-)-BCH \) alone, and both L-glutamine and \( \beta(-)-BCH \) were not tested within the same experiment(s). In such a case, the experimental values were normalized relative to the mean basal value found within the same experiment(s) and converted back to absolute values taking into account the overall mean basal reading derived from all available experiments.

For measurement of glutaminase activity (EC 3.5.1.2), groups of 450 islets each were sonicated (twice for 5 s) in 0.3 ml of a bicarbonate-buffered medium (Na\(^+\), 24 K\(^+\), 120 Mg\(^+\), 1 Ca\(^+\), 1 Cl\(^-\), 124 HCO\(_3\)\(^-\), 24 mM) containing bovine albumin (2 mg/ml) and equilibrated against a mixture of CO\(_2\) and O\(_2\) (5%/95%, v/v; pH 7.4). An aliquot of the homogenate (15 ml) was mixed with an equal volume of a solution containing L-glutamine (20 mM), and when required 2-ketoglutarate (up to 2 mM), and prepared in the same buffer. After a 20-min incubation at 37 \(^\circ\)C, the reaction was stopped by heating for 4 min at 90 \(^\circ\)C. After centrifugation, an aliquot (20 ml) of the supernatant was mixed with an equal volume of a solution which consisted of a Tris-
RESULTS

Insulin Release—Fig. 1 illustrates the enhancing action of L-glutamine, in increasing concentrations, upon insulin release evoked by \( \beta(\pm)\text{BCH} \) (20 mM). At a 1.0 mM concentration, L-glutamine doubled the insulinotropic action of \( \beta(\pm)\text{BCH} \). This near physiological concentration of L-glutamine was used in all further studies. The effect of increasing concentrations of \( \beta(\pm)\text{BCH} \) upon insulin release in the present system was previously characterized (2).

Glutamine Deamidation—The metabolic changes evoked by either L-glutamine (1 mM) or \( \beta(\pm)\text{BCH} \) (20 mM) relative to basal value have been described and analyzed in two recent publications (2, 15). Therefore, emphasis is here given to the metabolic situation found in the simultaneous presence of both amino acids. Nevertheless, the basal data and those collected in the presence of either L-glutamine or \( \beta(\pm)\text{BCH} \) are also presented for purpose of comparison.

Although \( \beta(\pm)\text{BCH} \) significantly augmented \( \text{NH}_4^+ \) production in islets not exposed to any other nutrient, the leucine linear with time, values of 114.0 ± 11.8 pmol/60 min/islet by adding NaOH (1.0 ml; 6 n) and heating the tubes at 60 °C for 10 min. The readings were corrected for the blank value (no homogenate) obtained at the same concentration of L-glutamine and 2-ketoglutarate, and expressed as mmol/60 min/islet by reference to appropriate \( \text{NH}_4^+ \) standards treated in the same manner as the reaction mixture.

All results are expressed as the mean ± S.E. together with the number of individual observations. The statistical significance of differences between mean values was tested by use of Student's t-test. The S.E. on the sum or difference between mean values was calculated according to Snedecor (14).

Effects of L-glutamine and \( \beta(\pm)\text{BCH} \) upon the islet output and/or content of metabolites

All results are expressed as pmol/60 min/islet. The statistical indices in the footnotes refer to the effect of L-glutamine (second column) or \( \beta(\pm)\text{BCH} \) (third column) relative to basal value (first column), and to the effect of \( \beta(\pm)\text{BCH} \) in the presence of glutamine (fourth column) relative to results found in the sole presence of glutamine (second column).

**Table I**

| Metabolite          | Control, no \( \beta(\pm)\text{BCH} \) | 1.0 mM L-glutamine, no \( \beta(\pm)\text{BCH} \) | 20.0 mM L-glutamine, no \( \beta(\pm)\text{BCH} \) | 20.0 mM L-glutamine, \( \beta(\pm)\text{BCH} \) |
|---------------------|----------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| Glutamate           | 10.3 ± 1.7 (14)                        | 57.9 ± 3.7 (14)*                            | 6.2 ± 0.8 (14)                              | 40.6 ± 3.4 (14)*                            |
| Malate              | 0.84 ± 0.16 (7)                        | 1.85 ± 0.36 (7)*                            | 1.85 ± 0.19 (7)*                            | 2.87 ± 0.24 (7)*                            |
| Oxaloacetate        | 5.52 ± 0.89 (11)                       | 11.64 ± 1.33 (11)*                          | 8.87 ± 0.88 (11)*                           | 13.75 ± 1.18 (11)                           |
| Pyruvate            | 17.2 ± 1.7 (11)                        | 28.4 ± 1.5 (11)*                            | 15.7 ± 0.9 (10)                             | 24.8 ± 1.2 (11)                             |
| Alanine             | 14.3 ± 2.4 (20)                        | 26.3 ± 2.9 (19)*                            | 10.8 ± 2.0 (18)                             | 25.3 ± 2.1 (20)                             |

*p < 0.001.

*p < 0.05.

*p < 0.005.

*p < 0.02.

*p < 0.025.

| Metabolite          | No \( \beta(\pm)\text{BCH} \) | No \( \beta(\pm)\text{BCH} \) | No \( \beta(\pm)\text{BCH} \) | No \( \beta(\pm)\text{BCH} \) |
|---------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Glutamate           | 114.0 ± 5.1 (31)*             | 57.0 ± 2.5 (15)*              | 100.7 ± 3.3 (23)*             | 40.6 ± 3.4 (14)*              |
| Malate              | 57.9 ± 3.7 (14)*              | 8.2 ± 0.8 (14)                | 40.6 ± 3.4 (14)*              | 2.87 ± 0.24 (7)*              |
| Oxaloacetate        | 11.64 ± 1.33 (11)*            | 8.87 ± 0.88 (11)*             | 13.75 ± 1.18 (11)             | 13.75 ± 1.18 (11)             |
| Pyruvate            | 28.4 ± 1.5 (11)*              | 15.7 ± 0.9 (10)               | 24.8 ± 1.2 (11)               | 24.8 ± 1.2 (11)               |
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*p < 0.001.

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The rate of glutamate conversion to 2-ketoglutarate by the reaction catalyzed by glutamate dehydrogenase in islets exposed solely to L-glutamine, i.e., about 14 pmol/60 min/islet (15). Such a comparison indicates that β(±)BCH increased by approximately 80% the flow rate through the reaction catalyzed by glutamate dehydrogenase.

Catabolism of 2-Ketoglutarate—In the islets exposed to L-glutamine, β(±)BCH failed to significantly affect the islet content and/or output of aspartate, malate, and pyruvate, the trend being here toward an increase in the content and/or output of these metabolites in response to β(±)BCH (Table I, 4th and 7th lines).

BCH increased the oxidation of L-[U-14C]glutamate by the islets. This increase amounted to +67.9 ± 15.0% (degree of freedom, 42; p < 0.001) after a 30-min incubation (Fig. 4). Thereafter, however, the stimulant action of β(±)BCH upon glutamate oxidation seemed to fade out. Indeed, between the 30th and 120th min of incubation, the lines characterizing the time course for 14CO2 output in the presence and absence of β(±)BCH, respectively, ran in parallel fashion, with a mean difference in elevation of 5.8 pmol/islet (expressed as L-glutamine residues).

Oxidation of Endogenous Fatty Acids—According to Fig. 2, β(±)BCH would augment O2 uptake by islets exposed to L-glutamine by 26.6 ± 5.9 pmol/60 min/islet. This represents no more than 5.5% of the basal O2 consumption in the present system (16) and would hardly account for the synergistic effect of the two amino acids upon insulin release. This apparent discrepancy between respiratory and secretory rates led us to investigate whether β(±)BCH and/or L-glutamine interfere with the oxidation of endogenous fatty acids, which may act as a fuel to cover part of the energy expenditure by islets deprived of exogenous nutrient (9, 10). The data summarized in Table II indicate that L-glutamine decreased by approximately 50% the output of 14CO2 from islets prelabeled with [U-14C]palmitate, whereas β(±)BCH slightly augmented 14CO2 output (p < 0.05). In the presence of both amino acids, the output of 14CO2 was lower than in the absence of exogenous nutrient (p < 0.05), but much higher than in the sole presence of L-glutamine (p < 0.001). These findings indicate that β(±)BCH antagonizes the sparing action of L-glutamate upon the oxidation of endogenous fatty acids (4).

If, as proposed elsewhere (7, 16), the latter oxidation accounts for 40% of the basal respiratory rate (486 ± 43 pmol of O2/60 min/islet), the effect of β(±)BCH upon 14CO2 output...
from islets prelabeled with [U-14C]palmitate and exposed to L-glutamine would correspond to an increase in
the islet content of adenine nucleotides and cyclic AMP (Table II). These findings are compatible with the view that the generation of reducing equivalents, the net uptake of Ca^{2+}, the activity of adenylate cyclase, and the release of insulin are somehow related in the process of nutrient-induced insulin release (11, 12, 18).

Our metabolic data indicate that \( \beta(\pm)BCH \) dramatically augmented the oxidative deamination of glutamate derived from exogenous glutamine (Fig. 2), in good agreement with the knowledge that \( \beta(-)BCH \) activates glutamate dehydrogenase in the islets (3). The activation of the enzyme coincided with an increased oxidation of L-[U-14C]glutamine (Fig. 4). The latter effect was most marked during the initial period of exposure to \( \beta(\pm)BCH \). It was previously shown that, in the absence of exogenous glutamine, the effect of \( \beta(\pm)BCH \) upon the consumption of \( O_2 \), oxidation of endogenous glutamate and net uptake of \( ^{45}Ca \) also tends to fade out during prolonged exposure to the leucine analog (2, 19).

In the absence of \( \beta(\pm)BCH \), the redox state of pyridine nucleotides and the concentration of ATP participate in the regulation of glutamine oxidation by the islets (15). Such was apparently also the case in the presence of \( \beta(\pm)BCH \), since menadione, which lowers the islet content of NADPH and NADH (11), augmented to the same extent the oxidation of L-[U-14C]glutamine whether in the absence or presence of \( \beta(\pm)BCH \). It should be stressed, therefore that \( \beta(\pm)BCH \) augmented glutamate oxidation, despite a concomitant increase in the islet ATP content and NADPH/NADP^+ ratio.

Table III

| ATP + ADP + AMP (pmol/islet) | No L-glutamine, no \( \beta(\pm)BCH \) | 1.0 mM L-glutamine, no \( \beta(\pm)BCH \) | No L-glutamine, 20.0 mM \( \beta(\pm)BCH \) | 1.0 mM L-glutamine, 20.0 mM \( \beta(\pm)BCH \) |
|-----------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| ATP (% of total)            | 15.2 ± 1.3 (15)                     | 16.5 ± 1.9 (18)                     | 15.8 ± 1.2 (15)                     | 15.7 ± 1.5 (15)                     |
| ADP (% of total)            | 43.0 ± 2.5 (15)                     | 36.3 ± 2.0 (18)                     | 66.9 ± 2.0 (15)                     | 55.1 ± 4.7 (13)^a                   |
| AMP (% of total)            | 34.5 ± 2.4 (15)                     | 35.0 ± 1.5 (18)                     | 23.9 ± 2.2 (15)^c                   | 26.4 ± 2.6 (13)                     |
| AMP/ADP (ratio)             | 22.6 ± 2.3 (15)                     | 28.7 ± 1.8 (18)^c                   | 9.1 ± 1.9 (15)^d                    | 18.5 ± 4.3 (13)^d                   |
| ATP/ADP (ratio)             | 1.40 ± 0.19 (15)                    | 1.11 ± 0.09 (15)                    | 3.17 ± 0.34 (15)^a                  | 2.42 ± 0.40 (13)                    |
| Adeylate charge (ratio)     | 0.603 ± 0.020 (15)                  | 0.577 ± 0.011 (18)^a                | 9.789 ± 0.001 (15)^d                | 0.083 ± 0.043 (13)^a                |
| NADP^+ (fmol/islet)         | 933 ± 56 (18)                       | 941 ± 43 (18)                       | 1040 ± 47 (18)                      | 106 ± 51 (18)                       |
| NADH (fmol/islet)           | 863 ± 10 (18)                       | 92 ± 13 (18)                        | 110 ± 18 (18)                       | 128 ± 21 (18)                       |
| NADH + NADP (fmol/islet)    | 1989 ± 66 (18)                      | 1003 ± 58 (18)                      | 1154 ± 68 (18)                      | 1186 ± 71 (18)                      |
| NADH/NADP^+ (ratio)         | 0.076 ± 0.006 (18)                  | 0.079 ± 0.011 (18)                  | 0.082 ± 0.010 (18)                  | 0.091 ± 0.011 (18)                  |
| NADP^+ (fmol/islet)         | 192 ± 11 (35)                       | 168 ± 10 (18)                       | 196 ± 8 (18)                        | 170 ± 12 (26)                       |
| NADPH (fmol/islet)          | 176 ± 12 (35)                       | 161 ± 11 (19)                       | 184 ± 12 (18)                       | 237 ± 19 (26)^c                     |
| NADP^+ + NADPH (fmol/islet) | 368 ± 14 (35)                       | 328 ± 13 (19)                       | 380 ± 19 (18)                       | 407 ± 22 (26)                       |
| NADPH/NADP^+ (ratio)        | 0.921 ± 0.032 (35)                  | 0.990 ± 0.064 (19)                  | 0.980 ± 0.044 (18)                  | 1.424 ± 0.064 (25)^d                |
| ^{45}Ca net uptake (pmol/islet) | 1.51 ± 0.13 (10)               | 1.78 ± 0.15 (10)                    | 3.36 ± 0.23 (10)^d                  | 4.16 ± 0.24 (10)^d                  |
| Cyclic AMP (fmol/islet)     | 49.0 ± 8.8 (12)                     | 62.2 ± 13.2 (7)                     | 77.9 ± 8.9 (12)^d                   | 132.6 ± 17.3 (12)^d                 |

\( ^p < 0.005 \)
\( ^* p < 0.001 \)
\( ^* * p < 0.005 \)
\( ^* * * p < 0.009 \)
In addition to the activation of glutamate dehydrogenase, the influence of \(\beta(\pm)\)BCH upon islet metabolism was characterized by two rather unexpected features.

First, \(\beta(\pm)\)BCH inhibited the conversion of exogenous L-glutamine to glutamate. This is unlikely to be due to a decrease in the uptake of L-glutamine by the islet cells, since L-glutamine and \(\beta(\pm)\)BCH are not transported by the same carrier system (20). A possible explanation for the decrease in glutamine deamidation would be that the BCH-induced increase in the mitochondrial generation of 2-ketoglutarate results in inhibition of glutaminase, an enzyme reported to be also located in mitochondria (21, 22). This explanation is consistent with the fact, that, in the islets in other tissues (23), 2-ketoglutarate indeed inhibits glutaminase (Fig. 3).

The second unexpected feature consisted in the fact that \(\beta(\pm)\)BCH augmented the oxidation of endogenous fatty acids and counteracted the inhibitory effect of L-glutamine upon such an oxidation (Table II). In our opinion, this is a most important finding. Indeed, it was consistently observed that the capacity of nutrient secretagogues to stimulate insulin release cannot be adequately explained by their capacity to be metabolized in the islets, if one ignores the effect of these secretagogues upon the utilization of endogenous nutrients (4, 7, 9, 10, 24). Likewise, in the present experiments, the influence of \(\beta(\pm)\)BCH upon the metabolism of endogenous L-glutamine was not sufficient to account for the synergistic effects of these two amino acids upon insulin release. However, when allowance was made for the changes in the oxidation of endogenous fatty acids, the estimated increase in \(O_2\) uptake and the observed value for insulin release yielded values close to those expected from the usual relationship between these two variables (17).

We now wish to discuss the mechanism by which L-glutamine and \(\beta(\pm)\)BCH affect the oxidation of endogenous fatty acids. It is unlikely that the islet content in ATP (or oxidized pyridine nucleotides) represents a major regulatory factor. Thus, both \(\beta(\pm)\)BCH and L-leucine prevent the fall in ATP normally seen in islets deprived of exogenous nutrient (2, 24) and, nevertheless, these two amino acids exert opposite effects upon the output of \(^{14}CO_2\) from islets prelabeled with \(\text{[\text{U}-\text{C}]}\) palmitate (24). An alternative explanation would be that the availability of oxaloacetate as an acceptor of acetyl-CoA residues represents a rate-limiting factor in the oxidation of endogenous fatty acids. This explanation is supported by the following considerations. After correction for the value found in the presence of antimycin A, the oxidation of endogenous fatty acids is decreased by 62.0 ± 5.2 and 92.9 ± 6.1% in the presence of L-glutamine, 1.0 and 10.0 mM, respectively (4). This coincides with an increase in aspartate production of 11.2 ± 2.3 and 16.4 ± 2.2 pmol/60 min/islet (4). Thus, by diverting oxaloacetate to aspartate, L-glutamine may well decrease the availability of oxaloacetate for circulation in the Krebs cycle. The latter view is supported by both the observation that the islet content of oxaloacetate is indeed slightly reduced at the high concentration of L-glutamine (4) and the knowledge that, in the islets as in other tissues (25), L-glutamine decreases the flow rate in the segment of the Krebs cycle between oxaloacetate and 2-ketoglutarate (4). In mirror of such a situation, \(\beta(\pm)\)BCH increases the generation and further catabolism of 2-ketoglutarate without increasing aspartate production and, hence, may increase the availability of oxaloacetate. Last, in the presence of both L-glutamine and \(\beta(\pm)\)BCH and relative to the situation found in the sole presence of L-glutamine, the generation and further catabolism of 2-ketoglutarate is again increased (Fig. 2) whereas the production of aspartate tends to be decreased, thus leaving more oxaloacetate available for circulation through the Krebs cycle.

In conclusion, the present work demonstrates that the enhancing action of L-glutamine upon BCH-induced insulin release is attributable to the changes evoked by these two amino acids in the metabolism of nutrients in the islet cells. The present study affords direct support to the concept that the insulin secretory response to nutrients is tightly related to their capacity to stimulate catabolic events in the islet cells (5). In this respect, nutrients may act as a fuel and/or an enzyme activator (26). In other words, the combined effect of L-glutamine and \(\beta(\pm)\)BCH upon both islet metabolism and insulin release illustrates that the substrate-site and regulatory-site hypotheses for insulin release, as first defined by Randle et al. (27), are not necessarily exclusive of one another.

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F Malaisse-Lagae, A Sener, P Garcia-Morales, I Valverde and W J Malaisse

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