Influence of Arginine on Splanchnic Glucose Metabolism in Man

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SUMMARY

To examine the mechanism of the arginine-induced rise in blood glucose concentration, splanchnic glucose output (SGO) and precursor uptake were studied during i.v. infusion of arginine (30 g/30 min) with and without somatostatin infusion (500 μg/h, 90 min) in postabsorptive and in 60-h fasted healthy subjects. The hepatic venous catheter technique was employed.

In the postabsorptive state, arginine infusion was accompanied by an eightfold and a fivefold increment, respectively, in the hepatic venous concentration of insulin and glucagon; SGO doubled and blood glucose increased by 30%. After cessation of arginine infusion, SGO and blood glucose returned to basal levels within 30 min.

When both arginine and somatostatin were administered, glucagon rose threefold, whereas the insulin response was abolished. And while the rise in SGO during arginine infusion and its subsequent decline were uninfluenced by the simultaneous infusion of somatostatin, the rise in blood glucose was more pronounced and the glucose concentration remained elevated longer than in control studies without somatostatin. Splanchnic uptake of glucogenic precursors was uninfluenced by arginine infusion, with or without simultaneous somatostatin administration.

In the 60-h fasted group, arginine infusion was accompanied by a minimal increase in insulin but a fivefold elevation of the glucagon level. Combined arginine and somatostatin infusion did not boost insulin significantly but the glucagon level rose threefold above the basal value. Basal SGO was 55% lower than in the postabsorptive state, and it rose in response to arginine administration (+50%) as well as during combined arginine and somatostatin infusion (+80%). No significant change in splanchnic uptake of glucogenic precursors was observed during arginine infusion with or without somatostatin administration.

We conclude that (1) arginine infusion is accompanied by a rise in SGO and blood glucose due to arginine-induced stimulation of glucagon secretion, (2) the rise in SGO is caused primarily by glucagon-stimulated hepatic glycogenolysis, and (3) combined somatostatin and arginine administration is accompanied by a more marked rise in blood glucose due to hypoinsulinemia and reduced peripheral glucose utilization. DIABETES 28:126–131, February 1979.

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Accepted for publication 17 October 1978.

The stimulatory effect of arginine on both insulin and glucagon secretion is well established in intact man[1–3] as well as in the perfused pancreas preparation[4,5] and in isolated pancreatic islet cells.[6] Administration of arginine is accompanied by a rise in blood glucose and an augmented production as well as utilization of glucose.[1,7] These metabolic alterations have been interpreted as effects of the arginine-induced secretion of insulin and glucagon. This view is supported by the observation that arginine, given to a totally pancreatectomized subject, fails to induce an increase in blood glucose.[8,9] However, administration of arginine in combination with somatostatin, an agent capable of suppressing both insulin and glucagon secretion,[10,11] is reportedly accompanied by a greater rise in blood glucose than that seen in response to infusion of arginine alone.[12] Whether this was the result of augmented hepatic glucose output or was a consequence of diminished peripheral glucose utilization could not be determined. Moreover, no data are available concerning the influence of arginine on hepatic glycogenolytic and gluconeogenic processes in man. The present study was undertaken, therefore, to examine the effect of arginine administration on the splanchnic exchange of glucose and gluconeogenic precursors in man with and without simultaneous suppression of insulin and glucagon secretion by somatostatin. Studies were carried out in healthy postabsorptive subjects as well as in individuals who had fasted for 60 h. In the latter state the hepatic glycogen stores

are almost completely depleted[13] and hepatic glucose output reflects, essentially, gluconeogenesis.

METHODS

Nine healthy, adult males, aged 21–42 yr, participated in the study. All were within 10% of ideal body weight (based on Metropolitan Life Insurance Tables, 1959). There was no history of diabetes or liver disease. The subjects were informed of the nature, purpose, and possible risks inherent in the study before giving their consent to participate.

One group of subjects was studied after an overnight (12–14 h) fast. Catheters were inserted percutaneously into a peripheral vein, a brachial artery, and into a right-sided hepatic vein under fluoroscopic control. Blood samples for determination of substrate concentrations were drawn from the arterial and hepatic venous catheters. Measurements of hormone levels were performed in samples from the hepatic vein. Two types of studies were conducted. In series ARG (five subjects), after a basal period, arginine (1 g/min) was infused intravenously for 30 min. Blood sampling was performed at timed intervals before and during arginine infusion and was continued for 90 minutes after the end of infusion. Urine was collected after the end of the study for arginine determination. In a second series (ARG + SRIF, five subjects) somatostatin was infused for 90 min at a rate of 500 g/h. Between the 30th and 60th min of somatostatin infusion the same i.v. arginine load as in series ARG was administered. Blood sampling was performed by following the same protocol. Three of the subjects participated in both series.

A second group of subjects was studied after 60 h of fasting. Arginine infusion alone (series ARG, three subjects) and arginine infusion with additional somatostatin infusion (series ARG + SRIF, three subjects), as well as catheterization and blood sampling, were done the same way as described above. Two of the subjects participated in both series.

Hepatic blood flow was estimated by the constant infusion technique[14] using indocyanine green dye.[15] Splanchnic glucose and glucose precursor exchange were calculated as the product of the arteriovenous concentration differences and hepatic blood flow. L-arginine monochloride was obtained in a 10% aqueous solution (Vitrum AB, Stockholm, Sweden). The final dilution administered to the subjects was 6% (pH 5.9, osmolality 500 mosmol/kg). Sterile, pyrogen-free, cyclic somatostatin was supplied by Wyeth Laboratories, Radnor, Pa.

Analytic methods. Glucose was analyzed in whole blood by the glucose oxidase reaction.[16] Lactate,[17] pyruvate,[18] 3-hydroxybutyrate,[19] and alanine[20] were all determined enzymatically in whole blood. Arginine and ornithine in plasma were measured by an automated ion-exchange chromatographic method using Liquimat III (Kontron Scientific and Technical Instrumentation, Zürich, Switzerland) and a Pico-Buffer system (Durrum, Sunny Vale, California). Arginine in urine and blood urea concentration were estimated using colorimetric methods.[21,22] Immunoreactive insulin and glucagon were determined as reported previously.[12,23] The lower limit of assay sensitivity for insulin was 5 μU/ml. Standard statistical procedures[24] were employed by use of the paired *t* test when applicable. Data in the text, tables, and figures are given as means ± SE.

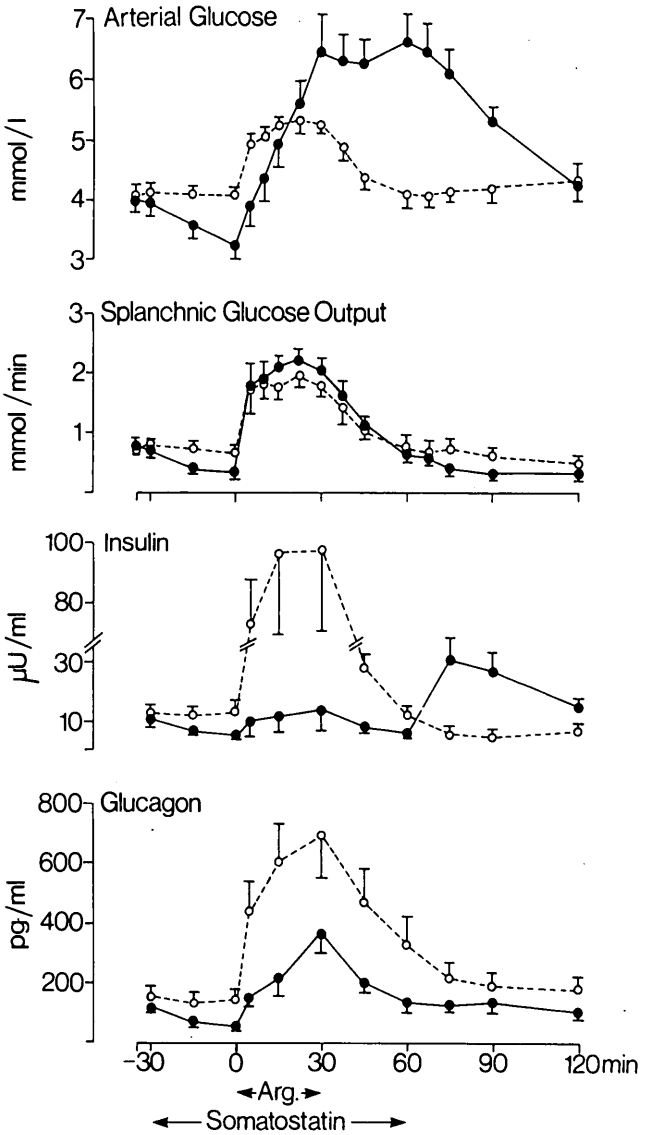

FIGURE 1. Effect of i.v. administration of arginine (30 g/30 min) without (○---○) and with (●——●) concomitant administration of somatostatin (500 μg/h, 90 min) on arterial glucose concentration and splanchnic glucose output as well as hepatic venous insulin and glucagon values in overnight fasted subjects (n = 5). Mean values ± SE are indicated.

RESULTS

POSTABSORPTIVE SUBJECTS

In series ARG, the concentrations of insulin and glucagon in hepatic venous plasma rose sixfold and threefold, respectively, after five minutes of arginine administration and reached peak levels eightfold and fivefold above basal after 30 min (Figure 1). In the postinfusion period, the concentration of insulin fell to baseline levels within 30 min and that of glucagon had done so at 60 min after the end of infusion.

The arterial blood glucose levels rose by 30% ($P < 0.001$) following arginine administration and declined to basal levels within 30 min after the end of the arginine infusion (Figure 1). Splanchnic glucose output (SGO) increased from 0.72 ± 0.04 mmol/min in the basal state to 1.71 ± 0.37 mmol/min ($P < 0.05$) after 5 min of arginine administration and remained at this level throughout the rest of the arginine

TABLE 1
Splanchnic uptake of glucogenic precursors and glucose output in the basal state as well as during and after arginine infusion with and without concomitant somatostatin infusion in 12-h- and 60-h-fasted subjects

	ARG			ARG + SRIF		
	Basal	30-min arginine infusion	30 min post-infusion	Basal	30-min arginine infusion	30 min post-infusion
			12-h-fasted subjects			
Splanchnic uptake of*		n = 5, mean SE			n = 5, mean SE	
Lactate (mmol/min)	0.13 ± 0.02	0.11 ± 0.02	0.11 ± 0.02	0.13 ± 0.02	0.13 ± 0.01	0.13 ± 0.01
Pyruvate (mmol/min)	0.010 ± 0.004	0.011 ± 0.006	0.009 ± 0.004	0.008 ± 0.004	0.013 ± 0.001	0.007 ± 0.001
Alanine (mmol/min)	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.06 ± 0.01	0.05 ± 0.01
Total	0.18 ± 0.02	0.16 ± 0.03	0.16 ± 0.03	0.19 ± 0.02	0.20 ± 0.02	0.19 ± 0.01
Splanchnic glucose output (mmol/min)	0.72 ± 0.04	1.68 ± 0.07	0.68 ± 0.02	0.73 ± 0.09	2.05 ± 0.20	0.70 ± 0.23
			60-h-fasted subjects			
Splanchnic uptake of*		n = 3, mean SE			Individual data for two subjects	
Lactate (mmol/min)	0.15 ± 0.02	0.13 ± 0.02	0.13 ± 0.02	0.13 0.15	0.15 0.11	0.10 0.17
Pyruvate (mmol/min)	0.010 ± 0.002	0.012 ± 0.001	0.008 ± 0.001	0.018 0.010	0.015 0.009	0.015 0.007
Alanine (mmol/min)	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.07 0.06	0.07 0.05	0.06 0.04
Total	0.20 ± 0.03	0.18 ± 0.03	0.18 ± 0.03	0.21 0.22	0.24 0.17	0.17 0.22
Splanchnic glucose output (mmol/min)	0.30 ± 0.02	0.46 ± 0.06	0.50 ± 0.09	0.33 0.27	0.48 0.63	0.33 0.36

* Data are given as glucose equivalents.

infusion period (Figure 1). Thereafter, SGO decreased steadily, returning to basal levels after 30 min.

In series ARG + SRIF, insulin fell to values below the lower limit of assay sensitivity (5 μU/ml), whereas glucagon levels fell by 60% ($P < 0.05$) during the initial phase with infusion of somatostatin alone. The arginine-induced rise in insulin was almost completely suppressed by somatostatin. In contrast, arginine-stimulated glucagon secretion reached peak levels three times above the basal level, corresponding to half the peak value in series ARG. Following cessation of somatostatin infusion, insulin rose rapidly to values threefold above the basal level. No rebound phenomenon was observed for glucagon.

The blood glucose concentration fell progressively from 4.01 ± 0.20 to 3.25 ± 0.25 mmol/ml during the initial period of only somatostatin infusion ($P < 0.001$, Figure 1). When arginine infusion was superimposed on somatostatin, the rise in blood glucose concentration during the arginine load was greater than in series ARG ($P < 0.005$). After cessation of arginine but with continuing somatostatin infusion the arterial glucose level remained elevated, exceeding the corresponding values in series ARG by 60% ($P < 0.001$). Somatostatin infusion alone resulted in a 55% decrease in SGO ($P < 0.005$). Neither the rise in SGO during arginine administration nor the decline after the end of infusion was affected significantly by concomitant somatostatin administration.

The basal arterial concentrations of pyruvate (0.06 ± 0.001 mmol/L), lactate (0.40 ± 0.03 mmol/L), and alanine (0.24 ± 0.01 mmol/L) were not significantly influenced by administration of either or both of arginine and somatostatin. Splanchnic glucose output and precursor uptake are shown in Table 1. Basal splanchnic uptake of the glucose precursors lactate, pyruvate, and alanine, calculated as glu-

TABLE 2
Effect of an arginine load on arterial concentrations and splanchnic exchange of arginine, urea, and ornithine in 12-h- and 60-h-fasted subjects

	Arterial concentrations			Splanchnic exchange		
	Basal	30-min arginine infusion	30 min post-infusion	Basal	30-min arginine infusion	30 min post-infusion
		mmol/L ± SE			mmol/min ± SE	
12-h-fasted subjects (n = 6)						
Arginine (plasma)	0.09 ± 0.01	8.25 ± 0.64	1.88 ± 0.15	0.01 ± 0.01	1.29 ± 0.17	0.30 ± 0.06
Urea (whole blood)	4.80 ± 0.45	5.44 ± 0.50	5.47 ± 0.42	−0.15 ± 0.04	−1.10 ± 0.14	−0.62 ± 0.13
Ornithine (plasma)	0.05 ± 0.01	0.54 ± 0.09	0.57 ± 0.10	0 ± 0.01	−0.19 ± 0.05	−0.12 ± 0.03
60-h-fasted subjects (n = 4)						
Arginine (plasma)	0.07 ± 0.01	7.08 ± 0.69	1.54 ± 0.44	0.02 ± 0.01	1.89 ± 0.39	0.49 ± 0.05
Urea (whole blood)	6.89 ± 0.64	8.20 ± 0.77	8.39 ± 0.98	−0.28 ± 0.07	−2.11 ± 0.38	−1.24 ± 0.14
Ornithine (plasma)	0.05 ± 0.01	1.62 ± 0.16	1.43 ± 0.12	0 ± 0.01	−0.73 ± 0.19	−0.33 ± 0.06

Data are presented from series ARG and series ARG + SRIF, which were calculated together.

cose equivalents, was 0.18 ± 0.02 mmol/min and remained essentially unchanged when arginine was infused with or without concomitant somatostatin infusion.

Arterial concentrations and splanchnic exchange of metabolites involved in the urea cycle are shown in Table 2. Arginine infusion was accompanied by a rise in the arterial plasma arginine concentration from 0.09 ± 0.01 to 8.25 ± 0.64 mmol/L at the end of the infusion; after that, the arterial concentration of arginine fell to 1.88 ± 0.15 at 30 min postinfusion. No net splanchnic exchange of arginine was observed in the basal state. Arginine administration resulted in a significant splanchnic uptake of arginine (1.29 ± 0.17 mmol/min) at the end of infusion. One-sixth of the arginine administered (5 g; range, 3–6 g) was excreted in the urine during the test period. Splanchnic urea output increased from 0.15 ± 0.004 in the basal state to 1.10 ± 0.14 mmol/min during arginine infusion, parallel with an increase of blood urea levels from 4.80 ± 0.45 to 5.44 ± 0.50 mmol/L by the end of arginine infusion. Arterial ornithine levels rose from 0.05 ± 0.01 in the basal state to 0.54 ± 0.09 mmol/L during arginine administration. No net splanchnic exchange of ornithine was detected in the basal state. After arginine infusion, splanchnic release of ornithine increased to 0.19 ± 0.05 mmol/min. Somatostatin did not significantly influence the arginine-induced changes in arginine, urea, and ornithine. The results from series ARG and ARG + SRIF are presented together, therefore, in Table 2.

Estimated splanchnic blood flow (ESBF) was 1.44 ± 0.09 L/min in the basal state and remained unchanged during and after arginine infusion. Somatostatin infusion alone (series ARG + SRIF) resulted in a 30% decrease ($P < 0.005$) in splanchnic blood flow (from 1.52 ± 0.08 to 1.09 ± 0.07 L/min). This level was maintained till the end of the somatostatin infusion, when it was followed by a rise to values slightly beneath those in the basal state.

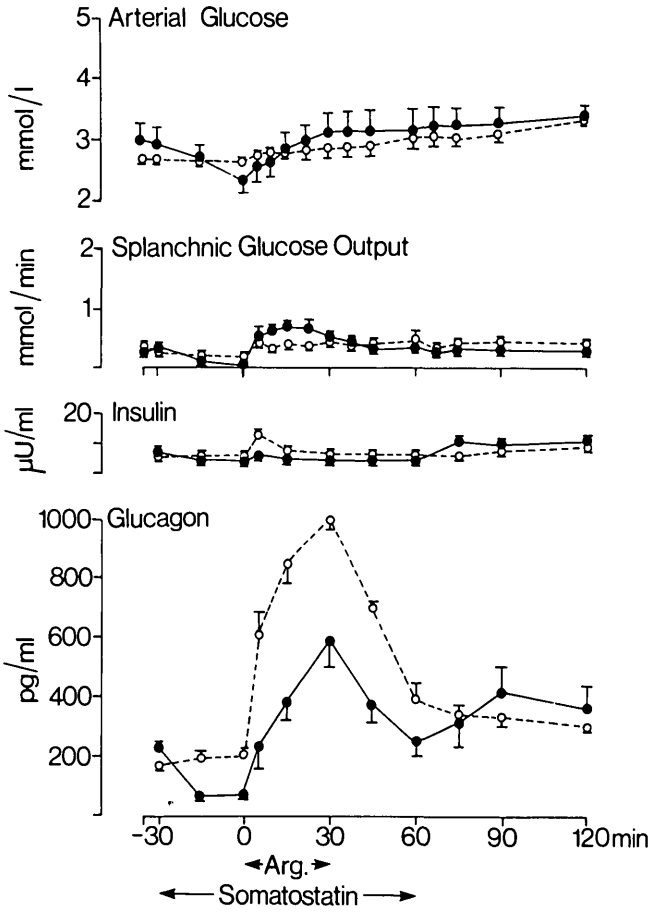

FIGURE 2. Effect of i.v. administration of arginine (30 g/30 min) without (○---○) and with (●——●) concomitant administration of somatostatin (500 μg/h, 90 min) on arterial glucose concentration and splanchnic glucose output as well as hepatic venous insulin and glucagon values in 60-h fasted subjects (n = 3). Mean values ± SE are indicated.

60-H-FASTED SUBJECTS

In the prolonged fasted group, the basal hepatic venous concentrations of insulin and glucagon did not differ significantly from those in the postabsorptive group, although the mean value for insulin was 50% lower and that for glucagon 60% higher. Arginine administration was accompanied by a twofold increase in insulin concentration within 5 min and a decline to basal levels thereafter (Figure 2). The peak value was only 13% of that in the 12-h-fasted group. The glucagon concentration rose fivefold when arginine was infused and was followed by a slow decline after the end of infusion. The changes were essentially similar to those of the overnight fasted individuals, although the mean peak value was higher (+40%). Basal arterial blood glucose concentration (2.65 ± 0.02 mmol/L) and splanchnic glucose output (0.30 ± 0.02 mmol/min) were 33% ($P < 0.001$) and 60% ($P < 0.01$) lower than in the overnight fasted group, respectively (Figure 2). Arginine administration (series ARG) led to a rise in SGO from 0.30 ± 0.02 to 0.46 ± 0.06 mmol/min and a minimal increase in blood glucose concentration. After the end of arginine infusion, a further progressive rise in blood glucose concentration was observed, to values that exceeded the basal level by 25% ($P < 0.005$).

During somatostatin infusion alone (series ARG + SRIF) the insulin level (basal; 6.5 ± 0.2 μU/ml) fell to values below the lower limit of assay sensitivity (5 μU/ml) and the glucagon concentration declined from 230 ± 15 to 71 ± 3 pg/ml. The arginine-induced rise in insulin concentration was inhibited completely by somatostatin, whereas the glucagon concentration rose to values that exceeded the pre-somatostatin level by 150%. After the end of somatostatin infusion, a small increase in both insulin and glucagon concentration was observed in series ARG + SRIF. During the first 30 min of somatostatin infusion alone, arterial glucose concentration declined progressively from 2.94 ± 0.16 to 2.29 ± 0.16 ($P < 0.05$) mmol/L, parallel with a fall in SGO from 0.33 ± 0.03 to 0.07 ± 0.01 mmol/min ($P < 0.05$). Arginine administration with ongoing somatostatin infusion was accompanied by an increase in SGO at 10–20 min of infusion, exceeding the corresponding SGO in the control study by 70–90% ($P < 0.05$), followed by a decrease to pre-somatostatin values before the end of arginine administration. The new level of SGO was maintained for the rest of the study period. The arterial glucose concentration rose to values slightly above those in series ARG, but the difference did not attain statistical significance.

Basal splanchnic uptake of gluconeogenic precursors did not differ from that in the overnight fasted group (Table 1). Blood levels and splanchnic exchange of lactate, pyruvate,

and alanine were unaffected by arginine infusion alone, and no appreciable change was observed when somatostatin was infused additionally. Estimated splanchnic blood flow (ESBF) was uninfluenced by arginine administration, whereas somatostatin infusion resulted in a 35% decrease ($P < 0.05$) followed by a slow increase to values slightly beneath pre-somatostatin ESBF within 15 min; after that, no further change in ESBF was observed. As in the overnight fasted group, somatostatin infusion did not affect the arginine-induced changes in either the arterial concentrations or the splanchnic exchange of urea, arginine, and ornithine. Series ARG and ARG + SRIF were, therefore, calculated together. During arginine infusion the mean value for splanchnic arginine uptake was slightly elevated (45%) and that of arterial arginine decreased by 15% compared with the overnight fasted group (Table 2). The differences did not attain statistical significance, however. Splanchnic output of urea and ornithine was twofold ($P < 0.05$) and fourfold ($P < 0.05$) higher, respectively, than after only an overnight fast. The ornithine concentration was increased threefold ($P < 0.001$) at 30 min of arginine infusion compared with overnight fasted individuals.

DISCUSSION

The present findings demonstrate that administration of arginine to human subjects is accompanied by marked increments in both insulin and glucagon concentrations (Figure 1). In agreement with previous observations,[1–3,12] the arginine-induced rise in glucagon concentration after 60 h of fasting was greater than that seen in overnight fasted individuals, whereas the insulin response was suppressed (Figure 2). Studies[3,25] both in vivo and in vitro have shown that a raised glucose concentration enhances the arginine-induced release of insulin, whereas that of glucagon is suppressed. In view of these findings, it is probable that the lowered blood glucose level in the 60-h fasted individuals contributed to the altered hormonal response to arginine administration seen in the present study.

Several studies in man have established the suppressive effect of somatostatin on both basal[10,11] and stimulated[26] insulin as well as glucagon secretion. The present findings show that somatostatin administration (500 μg/h) almost completely inhibits the arginine-induced secretion of insulin, whereas that of glucagon is incompletely suppressed (Figures 1 and 2). These differences in the suppressive action of somatostatin on arginine-stimulated insulin and glucagon secretion are probably dependent on dose and have also been demonstrated in vitro by use of isolated perfused rat pancreas.[27] Thus, our data indicate that somatostatin, in the dosage employed, fails to inhibit stimulated glucagon secretion when strong stimuli such as pharmacologic amounts of arginine are provided, as has been shown previously.[28]

The stimulating effect of glucagon on hepatic glucose production, even in the presence of mild to moderate elevations in insulin, is well documented in normal man.[28,29] It has been suggested that the observed increase in blood glucose concentration associated with administration of arginine is due to glucagon-mediated enhancement of hepatic glucose production.[30,31] In the present study, arginine administration to overnight fasted individuals was accompanied by a twofold increase in splanchnic glucose output. This was observed in parallel with a rise in glucagon concentration, thus supporting the above hypothesis. In series ARG + SRIF, somatostatin infusion did not completely inhibit the arginine-induced increase in glucagon values. The rise in splanchnic glucose output in response to arginine during ongoing somatostatin infusion is, therefore, most likely due to the increased glucagon concentration combined with the suppressed insulin response. The present findings, thus, indicate that the arginine-induced rise in blood glucose in overnight fasted subjects is due to a glucagon-stimulated splanchnic glucose output.

In series ARG, the arterial glucose concentration fell in parallel with the fall in splanchnic glucose output that followed cessation of the arginine infusion (Figure 1). In contrast, the blood glucose concentration rose more in series ARG + SRIF than in series ARG and remained elevated after the end of arginine administration. This was observed despite a decreasing splanchnic glucose output. The subsequent fall in blood glucose coincided with the end of somatostatin infusion and a rise in insulin concentration. Both the greater rise in arterial glucose concentration in response to arginine infusion and the hyperglycemia observed after the end of arginine administration are probably due to a diminished peripheral utilization of glucose secondary to the somatostatin-induced hypoinsulinemia.

The balance data for glucose and glucose precursors across the splanchnic bed are presented in Table 1. Uptake of glucose precursors was not influenced by either arginine alone or arginine combined with somatostatin. This finding suggests that the augmented hepatic gluconeogenesis from lactate, alanine, or pyruvate cannot be responsible for the observed increase in splanchnic glucose output during arginine administration. Splanchnic exchange of glycerol was not included in this study, but glycerol uptake in the basal state accounts for less than 10% of total precursor uptake.[11] Since arginine infusion is not known to stimulate lipolysis, it is unlikely that splanchnic uptake of glycerol increased during the arginine infusion.

In view of the consistent uptake of arginine by the splanchnic tissues during arginine infusion, one has to consider the possible contribution of this potentially glycogenic amino acid to splanchnic glucose output. However, when arginine was administered to 60-h fasted individuals (who are almost completely depleted of liver glycogen[13]), we demonstrated only a minimal increase in splanchnic glucose output, despite a considerable uptake of arginine. Furthermore, it has been shown by studies in vivo, employing both ^{14}C-arginine and the same arginine load as in the present study, that the conversion of arginine to glucose is a rather slow process.[30] This was indicated by the finding that labeled glucose did not appear until 30–50 min after the start of the arginine infusion. Consequently, the rapid rise in splanchnic glucose output in response to arginine in the present study cannot be due to arginine-derived glucose synthesis. Since uptake of other gluconeogenic precursors remained unchanged, it can be concluded that in the overnight fasted state, during which the hepatic glycogen stores are intact, the rapid increase in splanchnic glucose output in response to arginine is primarily a consequence of augmented hepatic glycogenolysis. Further sup-

port for this is obtained from the finding that arginine administration in the 60-h fasted subjects, with low hepatic glycogen concentration, failed to elicit a significant increase in splanchnic glucose output.

Administration of arginine was accompanied by about a 90 times increase in arginine concentration and a consistent uptake of this amino acid by the splanchnic area parallel with release of about an equimolar amount of urea (Table 2). These observations indicate rapid conversion of arginine to urea and ornithine by the arginase reaction. Since the splanchnic release of ornithine was minimal compared with the uptake of arginine, most of the ornithine is likely to have been retained in the liver. Possibly, ornithine may have been metabolized by a pathway different from the urea cycle, since splanchnic urea output did not exceed splanchnic arginine uptake, which otherwise would be expected.

It is noteworthy that the fractional extraction of arginine by the splanchnic tissues (13 ± 5%) was essentially uninfluenced by the marked rise in arginine concentration during arginine infusion. The present findings, thus, demonstrate that the human liver has a high capacity for both the extraction of arginine when the plasma concentration of this substance is raised and the conversion of this amino acid to urea and ornithine. This is in keeping with the demonstrated high activity of arginase in animal and human livers.[32]

In the 60-h fasted group, the splanchnic uptake of arginine as well as the release of urea and ornithine during arginine infusion were increased compared with the corresponding values in overnight fasted individuals. These changes resulted in a slightly smaller increase in arterial arginine concentration, a doubling of the rise in blood urea levels, and an increase in arterial ornithine concentration to values threefold above those seen after an overnight fast. Moreover, the fractional extraction of arginine by the splanchnic tissues (37 ± 5%) was increased compared with the overnight fasted group ($P < 0.05$). Concerning the possible background to these observations, starvation is known to exert a stimulatory effect on the concentration of enzymes involved in the urea cycle.[33] Thus, it is possible that the present findings may reflect starvation-induced alterations in intrahepatic amino acid metabolism.

REFERENCES

[1] Fajans, S. S., Floyd, J. C., Jr., Knopf, R. F., and Conn, J. W.: Effect of amino acids and protein on insulin secretion in man. Recent Prog. Horm. Res. *23*:617–62, 1967.

[2] Efendić, S., Cerasi, E., and Luft, R.: Role of glucose in arginine-induced insulin release in man. Metabolism *20*:568–79, 1971.

[3] Palmer, J. P., Walter, R. M., and Ensinck, J. W.: Arginine-stimulated acute phase of insulin and glucagon secretion. I. In normal man. Diabetes *24*:735–40, 1975.

[4] Iversen, J.: Secretion of glucagon from isolated, perfused canine pancreas. J. Clin. Invest. *50*:2123–36, 1971.

[5] Levin, S. R., Grodsky, G. M., Hagura, R., Smith, D. F., and Forsham, P. H.: Relationship between arginine and glucose in the induction of insulin secretion from the isolated perfused rat pancreas. Endocrinology *90*: 624–31, 1972.

[6] Chesney, T. McC., and Schofield, J. G.: Studies on the secretion of pancreatic glucagon. Diabetes *18*:627–32, 1969.

[7] Cherrington, A. D., and Vranic, M.: Effect of arginine on glucose turnover and plasma free fatty acids in normal dogs. Diabetes *22*:537–43, 1973.

[8] Barnes, A. J., and Bloom, S. R.: Pancreatectomized man; a model for diabetes without glucagon. Lancet *1*:219–21, 1976.

[9] Gerich, J. E., Karam, J. H., and Lorenzi, M.: Diabetes without glucagon. Lancet *1*:855, 1976.

[10] Koerker, D. J., Ruch, W., Chideckel, E., Palmer, J., Goodner, C. J., Ensinck, J., and Gale, C. G.: Somatostatin: hypothalamic inhibitor of the endocrine pancreas. Science *184*:482–84, 1974.

[11] Wahren, J., Efendić, S., Luft, R., Hagenfeldt, L., Björkman, O., and Felig, P.: Influence of somatostatin on splanchnic glucose metabolism in postabsorptive and 60-hour fasted humans. J. Clin. Invest. *59*:299–307, 1977.

[12] Waldhäusl, W., Bratusch-Marrain, P., Dudczak, R., and Deutsch, E.: The diabetogenic action of somatostatin in healthy subjects and in maturity onset diabetics. J. Clin. Endocrinol. Metab. *44*:876–83, 1977.

[13] Nilsson, L., Fürst, P., and Hultman, E.: Carbohydrate metabolism of the liver in normal man under varying dietary conditions. Scand. J. Clin. Lab. Invest. *32*:331–37, 1973.

[14] Bradley, S. E.: Measurement of hepatic blood flow. Methods Med. Res. *1*:199, 1948.

[15] Rowell, L. B., Blackmon, J. R., and Bruce, R. A.: Indocyanine green clearance and estimated hepatic blood flow during mild to maximal exercise in upright man. J. Clin. Invest. *43*:1677–90, 1964.

[16] Huggett, A. S. G., and Nixon, D. A.: Use of glucose oxidase, peroxidase, and o-dianisidine in determination of blood and urinary glucose. Lancet *2*:368, 1957.

[17] Wahren, J.: Quantitative aspects of blood flow and oxygen uptake in the human forearm during rhythmic exercise. Acta Physiol. Scand. *67* (Suppl. 269):1–93, 1966.

[18] Bücher, R., Czok, R., Lamprecht, W., and Latzko, E.: Pyruvate. *In* Methoden der enzymatischen Analyse. Bergmeyer, H. U., Ed. Weinheim, Verlag Chemie, 1962, p. 253.

[19] Williamson, D. H., Mellanby, J., and Krebs, H. A.: Enzymatic determination of D (−)-β-hydroxy-butyric acid and acetic acid in blood. Biochem. J. *82*:90–96, 1962.

[20] Karl, I. E., Pagliara, A. S., and Kipnis, D. M.: A microfluorometric enzymatic assay for the determination of alanine and pyruvate in plasma and tissues. J. Lab. Clin. Med. *80*:434–44, 1972.

[21] Micklus, J. M., and Stein, I. M.: The colorimetric determination of mono- and distributed guanidines. Anal. Biochem. *54*:545–53, 1973.

[22] Fawcett, J. K., and Scott, J. E.: A rapid and precise method for the determination of urea. J. Clin. Pathol. *13*:156–59, 1960.

[23] Waldhäusl, W., Haydl, H., and Novotny, P.: ACTH and cortisol responses to glucagon stimulation. J. Clin. Endocrinol. Metab. *43*:675–78, 1976.

[24] Snedecor, G. W., and Cochran, W. G.: Statistical Methods, 6th edit. Ames, Iowa State College Press, 1967.

[25] Leclercq-Meyer, V., Marchand, J., and Malaisse, W. J.: The role of calcium in glucagon release. Interactions between arginine and calcium. Horm. Res. *7*:348–62, 1976.

[26] Leblanc, H., Anderson, J. R., Sigel, M. B., and Yen, S. S. C.: Inhibitory action of somatostatin on pancreatic α and β cell function. J. Clin. Endocrinol. Metab. *40*:568–72, 1975.

[27] Efendić, S., Lins, P. E., Luft, R., Sievertsson, H., and Westin-Sjödahl, G.: Studies on the mechanism of somatostatin action on insulin release. Acta Endocrinol. (Copenhagen) *85*:579–86, 1977.

[28] Felig, P., Wahren, J., and Hendler, R.: Influence of physiologic hyperglucagonemia on basal and insulin-inhibited splanchnic glucose output in normal man. J. Clin. Invest. *58*:761–65, 1976.

[29] Wahren, J., Felig, P., and Hagenfeldt, L.: Effect of protein ingestion on splanchnic and leg metabolism in normal man and in patients with diabetes mellitus. J. Clin. Invest. *57*:987–99, 1976.

[30] Felig, P., and Marliss, E.: The glycemic response to arginine in man. Diabetes *21*:308–10, 1972.

[31] Cherrington, A. D., Kawamori, R., Pek, S., and Vranic, M.: Arginine infusion in dogs. Model for the roles of insulin and glucagon in regulating glucose turnover and free fatty acid levels. Diabetes *23*:805–15, 1974.

[32] Nuzum, C. T., and Snodgrass, P. J.: Urea cycle enzyme adaptation to dietary protein in primates. Science *172*:1042–43, 1971.

[33] Schimke, R. T.: Differential effects of fasting and protein-free diets on levels of urea cycle enzymes in rat liver. J. Biol. Chem. *237*:1921–24, 1962.