Brief Notes and Comments

The Glycemic Response to Arginine in Man

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SUMMARY

To determine the mechanism of the glycemic response to administration of arginine in man, incorporation of arginine-U-C-14 into blood glucose was investigated in postabsorptive subjects given an intravenous infusion of 30 gm. of L-arginine monochloride containing 50 μCi of L-arginine-U-C-14. As expected, a prompt increase in blood glucose and serum insulin levels was observed. However, whereas the maximal increment in blood glucose of 15 to 22 mg./100 ml. occurred within twenty to thirty minutes of initiation of the infusion, recovery of arginine-C-14 in blood glucose was not detectable until after thirty to fifty minutes, reaching peak levels at 120 min. In subjects given only the tracer dose of arginine-C-14 in whom serum insulin concentration remained at postabsorptive levels, incorporation of C-14 into blood glucose was detectable within ten minutes.

It is concluded that the glycemic effect of arginine cannot be explained on the basis of gluconeogenesis from this amino acid. The insulinogenic action of arginine may contribute to the delay in incorporation of this amino acid into glucose. DIABETES *21*:308-10, May, 1972.

In recent years, the intravenous infusion of arginine has become a useful clinical tool for stimulating insulin,[1] growth hormone,[2] and glucagon[3,4] secretion. In addition to these potent effects as an endocrine secretogogue, administration of arginine uniformly results in a measurable increment in blood glucose. With doses of approximately 30 gm. of arginine, mean maximal increases in blood glucose of 16 to 29 mg./100 ml. have been reported in normal subjects within twenty to thirty minutes of initiation of the infusion.[1,4] Greater increments have been observed in diabetic patients.[5] Despite the consistency of these effects, the mechanism of the glycemic response to arginine has not been established. Specifically the question has not been solved as to whether rapid conversion of this potentially glycogenic amino acid to glucose or alternatively stimulation of glycogenolysis, is responsible for the rise in blood glucose. Were the former possibility correct, the glycemic response to arginine could provide an index of hepatic gluconeogenic potential of use in evaluating a variety of abnormalities of glucose homeostasis.

The present study was consequently designed to determine the rapidity and magnitude of the conversion of exogenous arginine to glucose in postabsorptive man. To do this we have examined the incorporation into blood glucose of C-14 from a tracer dose of labeled arginine administered in conjunction with 30 gm. of the unlabeled amino acid. The data indicate that the prompt increment in blood glucose induced by arginine cannot be explained on the basis of gluconeogenesis from this amino acid.

METHODS

The subjects were five healthy male physicians, twenty-eight to thirty-two years of age. They weighed 140 to 180 lb. and were within 10 per cent of ideal body weight (Metropolitan Life Insurance tables, 1959).

The studies were carried out between 8 and 11 a.m. with the subjects in the recumbent position, after an overnight (twelve- to fourteen-hour) fast. Indwelling needles were placed in both antecubital veins and kept patent with a slow infusion of 0.9 per cent sodium chloride. In three subjects, following a control period of thirty minutes, 600 ml. of a 5 per cent solution (30 gm.) of L-arginine monohydrochloride* containing 50 μCi of L-arginine-U-C-14† (SA > 220 mCi/mmole) was infused intravenously at a constant rate over thirty minutes. In two additional subjects 50 μCi of L-arginine-U-C-14† was administered intravenously over thirty minutes in 600 ml. of 0.9 per cent sodium chloride. In all subjects venous blood samples were drawn at ten to thirty minute intervals during the control period and for 180 min. following initiation of the infusion.

Blood glucose was determined by the Technicon Auto-Analyzer ferricyanide procedure.[6] Serum insulin was measured by radioimmunoassay, employing the double antibody technic.[7] To determine the radioactivity of blood glucose, the periodate oxidation method of Reichard et al.[8] was employed, in which the CO_2 derived from carbons 1-5 of glucose is isolated as $BaCO_3$ and the formaldehyde derived from carbon 6 is isolated as the formaldimedone. The procedures for

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counting the $BaCo_3$ and the formaldimedone have been described previously.[9] The data on blood glucose radioactivity (figures 1 and 2) are expressed as the total counts in both fractions (carbons 1-5 plus carbon 6). Since no data were available to exclude the possibility that periodate oxidizes arginine, preliminary studies were undertaken in which it was demonstrated that periodate oxidation of whole blood to which arginine-C-14 had been added in vitro did not result in the recovery of C-14 as $BaCo_3$ or formaldimedone.

RESULTS

In figure 1 the blood glucose response to infusion of 30 gm. of arginine and the incorporation of arginine-U-C-14 into blood glucose are shown. Blood glucose rose during the first ten minutes of the infusion and reached maximal increments of 15 to 22 mg./100 ml. within twenty to thirty minutes. In marked contrast, recovery of C-14 from arginine in blood glucose was not detectable until thirty to fifty minutes after initiation of the infusion. Furthermore, maximum incorporation of arginine-C-14 into blood glucose did not occur until after 120 min. As anticipated,[1,4] serum insulin rose promptly following arginine infusion, reaching maximal increments of 35 to 125 μU./ml. (figure 1).

To determine if the delay in appearance of arginine-C-14 in blood glucose in the subjects receiving the 30 gm. dose of arginine was a consequence of the increment in serum insulin levels, two subjects were given a tracer dose of arginine-C-14 without any of the unlabeled amino acid. As shown in figure 2, arginine incorporation into blood glucose was detectable in both subjects within ten minutes of initiation of the infusion. In these subjects serum insulin levels remained stable at 12 to 16 μU./ml. and blood glucose fluctuated by less than 5 mg./100 ml. throughout the period of study.

DISCUSSION

The present findings confirm the prompt glycemic response to arginine infusion in man. The data, however, also indicate that the blood glucose increment cannot be accounted for on the basis of gluconeogenesis from the administered substrate. Whereas peak increments in blood glucose were observed within twenty to thirty minutes of initiation of the infusion, arginine-C-14 incorporation into blood glucose was not detectable until after thirty to fifty minutes, with maximum recovery occurring at 120 min. That the increment in serum insulin induced by a 30 gm. dose of arginine may be responsible for the delay in conversion of this amino acid to glucose is suggested by the more rapid appearance of arginine-C-14 in blood glucose in the subjects receiving the tracer dose

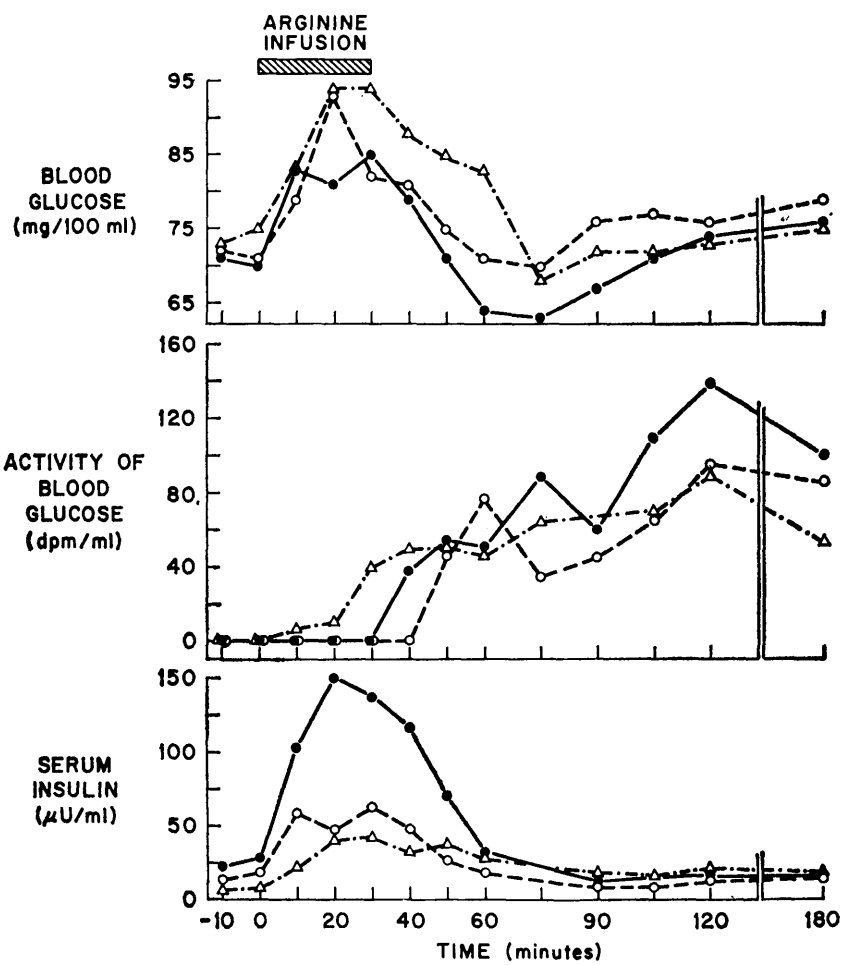

FIGURE 1

Blood glucose and serum insulin response and incorporation of C-14 into blood glucose following infusion of 600 ml. of 5 per cent L-arginine monochloride containing 50 μCi of L-arginine-U-C-14.

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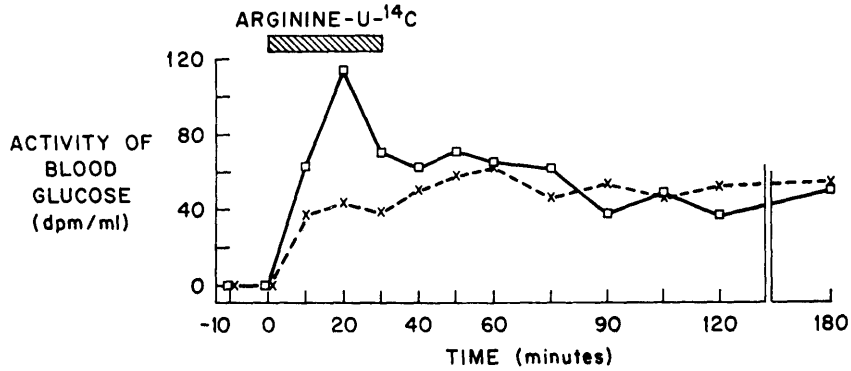

FIGURE 2

Incorporation of C-14 into blood glucose following infusion of 50 μCi of L-arginine-U-C-14 administered over thirty minutes in 0.9 per cent sodium chloride. Blood glucose and serum insulin levels measured at ten- to thirty-minute intervals, fluctuated by less than 5 mg./100 ml. and 4 μU./ml., respectively, throughout the period of study.

alone in whom serum insulin concentration remained at basal, postabsorptive levels. However, the lack of a significant increment in the arginine pool size in the subjects receiving only the tracer dose may also contribute to the more rapid incorporation of C-14 into glucose.

Since rapid gluconeogenesis cannot be invoked as the explanation for the prompt increase in blood glucose following arginine administration, alternative mechanisms must be considered. The demonstration that arginine stimulates glucagon,[3,4] as well as insulin secretion raises the possibility that glycogenolysis is responsible for the blood glucose elevation. Supporting a glycogenolytic effect is the observation that a three to four-day fast, which has been demonstrated to result in virtually complete dissipation of liver glycogen stores,[10] causes a marked attenuation of the glycemic response to arginine despite evidence of augmented glucagon and diminished insulin secretion.[11]

The persistence of a glycogenolytic effect despite inhibition of gluconeogenesis following aminogenic stimulation of both alpha and beta cell secretion is also consistent with the relative sensitivity and known interaction of glucagon and insulin. Thus it has been demonstrated that the glycogenolytic effect of glucagon may be observed at concentrations of this hormone which fail to stimulate gluconeogenesis.[12,13] Furthermore, physiologic increments in insulin concentration may inhibit glucagon-induced urea production but fail to inhibit glucagon-stimulated glycogenolysis.[14] Thus while rapid gluconeogenesis from arginine is prevented by the insulinogenic effect of this amino acid, it is possible that a concomitant increment in glucagon results in glycogenolysis which is responsible for the prompt rise in blood glucose.

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