Effect of Glucose Priming on Insulin Response in the Premature Infant

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SUMMARY

Our paper deals with premature infants in the first twenty-four hours of life and reports the effect of a preinfusion of glucose on glucose administration. Glucose infusion (2.5 gm.) resulted in a slight elevation of serum insulin. When this administration of glucose was preceded by a two-hour infusion of glucose, there was a striking increase in serum insulin. DIABETES *24*:291-94, March, 1975.

The fetus in utero is continuously perfused with glucose acquired transplacentally and fetal blood glucose levels fluctuate with those of the mother.[1] The fetal blood sugar is normally low (70-80 per cent of that of the mother) and falls even lower during the neonatal period.[2,3]

Insulin is present in the fetal pancreas as early as the tenth to twelfth gestational week and there is a progressive increase in insulin content up to the time of birth.[4,5] However, although some discrepancy is to be found in the literature,[6] it has been repeatedly demonstrated that glucose is a poor stimulant of insulin secretion throughout fetal life[7] and during the immediate neonatal period.[8,9] A possible explanation for this low insulin response to glucose remains to be determined. However, this does not seem to depend on an immaturity of the beta cell as amino acids[10-12] cause a marked and rapid increase of insulin release. Moreover, it has been seen that the activity of the beta cell is markedly influenced by maternal hyperglycemia during diabetes. Infants of diabetic mothers display islet cell hyperplasia and hypertrophy,[13,14] increased insulin content[4,14] and an increased beta cell responsiveness to glucose.[15,16]

Our aim was to determine the influence of a preinfusion of glucose on the effect of an infusion of glucose on insulin release in the premature infant.

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MATERIAL AND METHODS

Twenty-five vaginally delivered premature children were studied. Their prematurity was based on clinical examination and gestational age,[17,18] this being 34.1 ± 0.3 weeks (Mean ± S.E.M.), while their weight was 2,220.0 ± 43.5 gm. At times varying from two to twenty-three hours after birth, and before feeding was initiated, a polyethylene catheter was inserted in the umbilical vein to withdraw blood samples and administer infusions.

Two groups of infants received an intravenous infusion of 2.5 gm. of glucose over a thirty-minute period. In the first group of twelve infants, a total of 920 mg. of glucose was administered over a two-hour period at the following rate: 125 mg. given acutely followed by 15 mg. per minute for thirty minutes, 5.5 mg. per minute for thirty minutes, and 3 mg. per minute for sixty minutes. This was immediately followed by a thirty-minute infusion during which period the infants received 2.5 gm. of glucose.

The control infants, a group of thirteen, received a two-hour infusion of physiological saline just prior to the thirty-minute infusion of a total of 2.5 gm. of glucose.

The mean age at testing was 13.2 ± 1.9 hrs. (range two to twenty-three hours) in the group preinfused with glucose and 12.7 ± 0.6 (range two to twenty-one hours) in the control group. On each occasion the nature and the aim of the investigation were explained to the parents and were carried out with their consent.

Blood was collected for glucose determination in tubes containing sodium fluoride. Glucose was measured by a glucose oxidase method (Sigma Chemical Co., St. Louis, Mo.). Insulin was determined in triplicate by the immunochemical method of Hales and Randle[19] using human insulin as reference standard.

RESULTS

Effect of a preinfusion of glucose on 2.5 gm. infusion of glucose (figure 1). During the two-hour preinfusion of glucose in the twelve infants with body weight of 2,180.0 ± 70 gm., the blood sugar level rose from 54 ± 2 mg. at −120 min. to 97 ± 8 mg. per 100 ml. at −90 min. and then decreased gradually to 73 ± 3.7 mg. per 100 ml. at 0 min. Serum insulin rose during this period from 8.2 ± 1.5 μU. per ml. at −120 min. to 15.6 ± 2.3 μU. per ml. at 0 min. The successive, rapid 2.5 gm. glucose infusion caused the blood sugar to go up acutely from 73 ± 3.7 mg. at 0 min. to 248.2 ± 14.7 mg. per 100 ml. at 30 min. and then fall to 185.2 ± 15.9 mg. and 88.7 ± 4.7 mg. per 100 ml. at sixty and 120 min., respectively. Serum insulin rose from 15.6 ± 2.3 μU. per ml. at 0 min. to 42.7 ± 12.7 μU. per ml. at 30 min. and 93.6 ± 23.8 μU. per ml. at 60 min. and then decreased to 67.5 ± 13.9 μU. per ml. at 120 min. Maximal increase occurred at 30 min. in one subject, at 60 min. in seven subjects, and at 120 min. in four subjects.

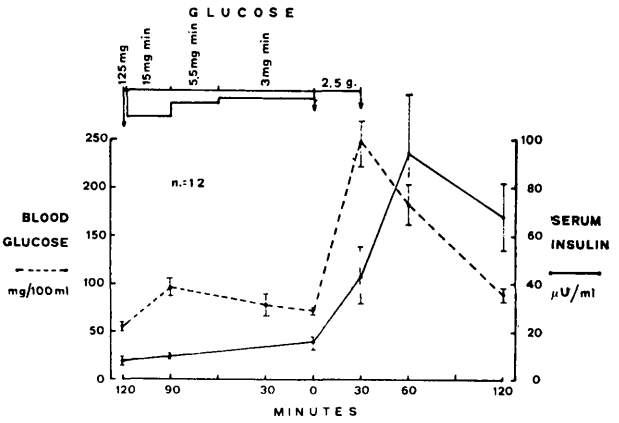

FIG. 1. Effect of a preinfusion of glucose on a 30 min. infusion of glucose.

Effect of a preinfusion of saline on 2.5 gm. infusion of glucose (figure 2). During the two-hour preinfusion of saline in thirteen infants with body weight of 2,256.9 ± 40 gm., the blood sugar and serum insulin remained almost unchanged.

However, the successive rapid 2.5 gm. of glucose infusion caused the blood sugar to go up acutely from 58 ± 4 mg. at 0 min. to 246 ± 14 mg. per 100 ml. at 30 min. and then fall gradually to 168 ± 14 mg. and 89 ± 12 mg. per 100 ml. at 60 and 120 min., respectively. But the serum insulin went up only from 6.4 ± 1.2 μU. per ml. at 0 min. to 9.8 ± 2 and 18.2 ± 4.7 μU. per ml. at 30 and 60 min., respectively, and remained constant until 120 min.

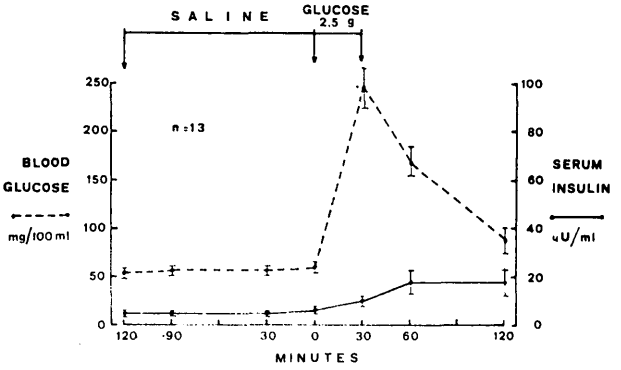

FIG. 2. Effect of a preinfusion of saline on a 30 min. infusion of glucose.

DISCUSSION

Our data demonstrate that glucose causes a small increase in serum insulin in the premature infant. But if an infusion of glucose precedes the acute injection, it becomes a potent stimulus of insulin secretion. However, the blood glucose curves in both groups of infants resemble each other closely in spite of the great difference in the insulin curves.

In both full-term and premature infants the disappearance rate of glucose from the blood is much slower than that in older infants,[20] and this low disposal has often been correlated with a reduced and delayed rate of insulin secretion.[8,16] However, the data of the present work do not seem to bear out this hypothesis. It seems that glucose disposal in our premature infants is influenced by other factors than simply by changes in insulin levels as demonstrated in low birth weight infants and newborn animals. In fact a high removal rate of glucose during the first day of life is seen in hypoglycemic infants small for gestational age, irrespective of whether they have high or normal insulin secretion.[21] Furthermore, Gentz et al.[22] showed that low birth weight newborn infants cleared intravenously administered glucose at the same rate if they showed an insulin response or not. In fed newborn piglets[23] and rats[24] glucose induces a greater insulin response in fed animals than in fasting ones. However, this marked increase in insulin response in fed animals is not accompanied by a greater increase in glucose disappearance rate.

It is unknown whether the priming action of the small amount of glucose administered in our infants is a consequence of its role as energy source or due to

other unknown effects of the glucose molecule. Studies have shown that glucose can also serve as substrate in the oxidative metabolism of the beta cell and energy made available to the cell during the breakdown of this substance is utilized to drive the specific secretory mechanism and the synthetic process in the beta cell.[25,26] In vitro,[27] and in vivo[28] studies have also indicated that a critical level of glucose (70-90 mg. per 100 ml.) is required for glucose to stimulate insulin secretion. In this context the prolonged lower blood glucose concentration of the normal newborn and fetus may be a factor that determines the attenuated insulin response. However, in our control group, infants with blood glucose similar to or approaching that of the adult have a similar response.

The insulin secretion pattern seen in our premature infants bears some resemblance to that seen in fasting rats as reported by Grey et al.[29] The authors reported that these animals exhibited a marked impairment in the insulin secretory response to glucose while a normal mobilization of this hormone was evoked by theophylline. This abnormality could be ameliorated by the intermittent administration of small doses of glucose during fasting. On the basis of these findings they suggested that the beta cell possesses a glucose-inducible glucoreceptor concerned with the regulation of insulin release.

The data obtained from our studies concern infants after they had undergone delivery and were adjusting themselves to extrauterine life. However, we think that slight changes in the magnitude of the fluctuation of the maternal glucose probably give rise to profound alteration in fetal insulin secretion. Asplund[30] observed that glucose administered to pregnant rats by intermittent infusion during the last five days of gestation reversed the fetal pancreatic unresponsiveness to glucose.

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