Glucose Homeostasis in the Neonate and Infant

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Glucose homeostasis in the preterm, term, and young infant can be considered from the perspective of either whole body or specific organ metabolism. One can evaluate the physiological control of glucose flux and the role of hormones and the nervous system in the maintenance of a stable blood glucose concentration; alternatively enzymatic control of specific substrates can be examined biochemically at the cellular or subcellular level. The discussion will concern primarily the former.

Over the past decade, increased use of stable isotope tracers have quantified glucose flux (turnover) under a variety of conditions. From the whole body perspective, newborn glucose turnover is approximately 4 to 6 mg kg\(^{-1}\) min\(^{-1}\). This contrasts with the postabsorptive adult whose glucose turnover approximates 2 to 3 mg kg\(^{-1}\) min\(^{-1}\). In the latter, approximately half of this is utilized by the brain, which occupies only 2% of total body mass. In contrast, the newborn has a relatively larger brain, which occupies about 12% of total body mass. If the newborn brain metabolized glucose as its sole energy source at a rate comparable to older children, a glucose turnover of 8 mg kg\(^{-1}\) min\(^{-1}\) would be necessary (1). The infant would theoretically utilize all of its hepatic glucose production to sustain cerebral metabolism. Since this is unlikely, an overestimate of neonatal cerebral metabolic requirement has probably occurred, or the cerebrum utilizes alternate substrates such as ketones and lactate (2).

To further compare the young infant with the adult, it is known that adipose tissue is virtually absent until the beginning of the third trimester when it accumulates rapidly. By term, the infant has 14% to 16% body fat. This contrasts with the adult whose body fat mass approximates 20% of total body mass in males and 30% in females. Nutritionally, it is apparent that the very low birth weight infant in the late second trimester, early third trimester has no fat energy reserves and depends on other tissues (i.e., muscle) as a source of energy substrate during starvation.

Like the brain, the neonatal liver mass is also increased, relative to the adult.
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Since glycogen stores in the fed state approximate 5 g percent, the neonatal liver could support glucose requirements from glycogen for about 5 hr. In contrast, the adult could sustain glucose requirements for about 25 hr.

We have focused on the brain as the major organ for metabolism of glucose and have related this to hepatic glycogen stores. Unfortunately, this simplistic view is incomplete. First, hepatic control of glucose is dependent both on glycogenolysis and gluconeogenesis, which are probably operative in the human newborn. Glycogen is present in the liver by 8 weeks of gestation, and the requisite enzymes for synthesis and degradation are already present. In isolated organ culture, human fetal liver from second-trimester fetuses responds to glucagon or cyclic AMP by glycogen degradation (3). The latter hormone and effector have also been shown to stimulate gluconeogenesis from $^{14}$C-alanine. Thus prior to fetal viability, glycogen deposition and degradation are well established as are hepatic glycolysis and gluconeogenesis. The two major hormones, insulin and glucagon, are already in the fetal circulation by 8 weeks of gestation. However, the remaining controls by the sympathetic nervous system and catecholamines (norepinephrine and epinephrine) are not fully mature.

Although enzymes and hormones necessary for glucose homeostasis are reasonably well developed, neonatal hepatic control is not as precise as in the adult. For example, the adult response to the administration of epinephrine or glucagon results in stimulation of a prompt (within minutes) release of glucose from glycogen as well as an early insulin release. In contrast, the neonate responds slowly over 60 to 120 min and requires a log higher dose of glucagon to achieve maximal response (4). Another difference is the response to a rapid infusion of glucose. In the adult, glucose infusion is associated with a two-phase insulin secretion: an initial rapid rise in peripheral plasma insulin concentration within 2 to 5 min followed by a slower and prolonged second-phase insulin release. Concomitant with the insulin release is a rapid disappearance and tissue uptake of glucose. The well newborn infant responds to injected glucose with a very slow rate of glucose disposal. Insulin secretion is highly variable; the initial early phase secretion is absent or blunted so the major insulin release occurs later (i.e., after 30 min) (Fig. 1) (5).

Grasso and associates have studied well premature infants extensively (6). A glucose load given intravenously for 30 min, sufficient to produce hyperglycemia, had minimal effects on the plasma insulin concentration. In contrast, infusion of a mixture of nine amino acids elicited a prompt insulin response. This hyperinsulinemia did not affect the blood glucose concentration. This group has shown that amino acid or glucose priming can influence the insulin response. In addition, the duration of the stimulus appears to be another important variable.

The term newborn responds differently than the adult does to insulinogenic amino acids such as arginine (7). The characteristic adult response is an elevation of plasma insulin concentration sustained during the 30-min arginine infusion. This is associated with a decrease in plasma free fatty acid concentration. Interestingly, plasma glucose is slightly increased. In contrast, 2 hr after delivery the newborn has a minimal insulin secretion. Nevertheless, this is sufficient to produce a
fall in plasma free fatty acid concentration (Fig. 2). The minimal insulin response may be related to the lower plasma glucose level found at this age. These observations may have significance for infants managed parenterally. Early admixture of amino acids with dextrose may be an advantage in terms of stimulating an endogenous insulin response.

Another characteristic of the adult is the response of the liver to exogenous glucose. Under postabsorptive conditions, the liver releases glucose from either glycogenolysis or from gluconeogenesis to meet peripheral tissue energy requirements. The elevation of plasma glucose from either the oral or parenteral administration of glucose results in a prompt and reciprocal decrease in hepatic output. When glucose administration exceeds hepatic output, the liver becomes a storage organ. Unlike the adult's precise control of plasma glucose concentration, the newborn has a variable response. Thus, preterm and some term infants have a continued hepatic glucose output even when exogenous glucose is administered at rates well above basal hepatic glucose output. This persistent hepatic glucose out-
put has been documented in newborn puppies as well as in lambs and in the human (8–10).

Our studies of hormonal and metabolic systems important in the developmental maturation of glucose homeostasis initially focused on the sensitivity of the liver (splanchnic bed) to glucose and insulin and concerned the heretofore described prompt diminution of the mature (adult) response to exogenous glucose infusion (9). We evaluated the validity of this hypothesis in the neonatal period in 26 unanesthetized mixed-breed lambs compared with eight 4- to 5-month-old mixed-breed sheep. After a 7 hr fast, basal plasma glucose, insulin, and glucagon concentrations were determined following which the term lambs received glucose as either 0, 5.7, 11.7, or 21.7 mg kg\(^{-1}\) min\(^{-1}\) continuously during 8 hr, whereas the 5-month-old sheep received glucose as either 0 or 5.7 mg kg\(^{-1}\) min\(^{-1}\). Following 14 hr of fasting, glucose turnover (production) was determined by the prime-constant infusion technique using \(^3\)H\(_6\) radiolabeled D-glucose during a 50-min turnover period that followed the 6-hr infusion of 0.45% saline or the varying doses of glucose. Both newborn and adult animals maintained a constant plasma glucose concentration and glucose specific activity during the turnover period. Table 1 denotes the plasma glucose, insulin, and glucagon concentrations and rates of glucose production in study subjects during the turnover period.
<table>
<thead>
<tr>
<th>Number</th>
<th>Glucose Infusion rate mg/kg/min age</th>
<th>Glucose mg/dl (mean ± SEM)</th>
<th>Steady state Insulin µU/ml (mean ± SEM)</th>
<th>Glucagon pg/ml (mean ± SEM)</th>
<th>Glucose turnover Total mg/kg/min (mean ± SEM)</th>
<th>Endogenous mg/kg/min (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>0 (3 days)</td>
<td>112 ± 23</td>
<td>5 ± 3</td>
<td>300 ± 41</td>
<td>—</td>
<td>7.4 ± 1.1</td>
</tr>
<tr>
<td>11</td>
<td>5.7 (3 days)</td>
<td>182 ± 18</td>
<td>31 ± 6</td>
<td>283 ± 56</td>
<td>10.4 ± 0.7</td>
<td>4.8 ± 0.7</td>
</tr>
<tr>
<td>4</td>
<td>11.7 (3 days)</td>
<td>238 ± 32&lt;sup&gt;b&lt;/sup&gt;</td>
<td>70 ± 16&lt;sup&gt;c&lt;/sup&gt;</td>
<td>265 ± 77</td>
<td>18.0 ± 1.8</td>
<td>6.4 ± 1.7</td>
</tr>
<tr>
<td>4</td>
<td>21.7 (3 days)</td>
<td>464 ± 23&lt;sup&gt;b&lt;/sup&gt;</td>
<td>270 ± 108&lt;sup&gt;d&lt;/sup&gt;</td>
<td>—</td>
<td>21.7 ± 1.3</td>
<td>0.6 ± 1.1</td>
</tr>
<tr>
<td>4</td>
<td>0 (4–5 months)</td>
<td>76 ± 6</td>
<td>15 ± 2</td>
<td>254 ± 25</td>
<td></td>
<td>2.8 ± 0.2</td>
</tr>
<tr>
<td>4</td>
<td>5.7 (4–5 months)</td>
<td>174 ± 29&lt;sup&gt;c&lt;/sup&gt;</td>
<td>56 ± 81&lt;sup&gt;b&lt;/sup&gt;</td>
<td>309 ± 20</td>
<td>6.6 ± 0.3</td>
<td>0.9 ± 0.3&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
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*Unpaired t-tests were performed between each infusion group and the 0.45% saline (0 glucose) group.

<sup>b</sup>p < 0.01
<sup>c</sup>p < 0.02
<sup>d</sup>p < 0.05

(From Cowett et al., ref. 9)
Glucose production persisted in the term lamb until the exogenous infusion reached four times the basal rate. In contrast, the adult lambs reduced the rate of glucose production with a glucose infusion rate of only twice the basal rate. Both rates were approximately two to three times the basal rate; however, this resulted in marked hyperglycemia in the newborn. At the time that the glucose production rate was significantly reduced, the plasma insulin level in the newborn lamb was fivefold greater than in the adult sheep (270 vs 56 μU/ml). We concluded that hepatic unresponsiveness to insulin may be a major factor responsible for the inefficiency in glucose homeostasis in the neonatal lamb (9).

In the initial studies, hyperinsulinemia and hyperglycemia were produced simultaneously, and thus the effect of peripheral hyperinsulinemia in contrast to a portal effect was not differentiated from that of hyperglycemia. To dissociate the effects of plasma glucose from plasma insulin in the control of hepatic glucose production, varying concentrations of glucose and insulin were infused in newborn lambs for sufficient time to produce steady state equilibrium conditions of euglycemia and hyperinsulinemia. Gluconeogenesis from lactate was also measured by determining the ratio of [3-14C] lactate to D-[3-3H]glucose, as noted by \( r \) in Fig. 3. In-

![Graph](image-url)
creasing the rates of glucose infusion without insulin administration (groups II and III) produced a stepwise increase in plasma glucose and insulin concentrations when compared with controls (group I). The elevation of plasma insulin induced by hyperglycemia was associated with a significant ($p<0.001$) reduction in the rate of glucose production. This was seen only when marked hyperglycemia and hyperinsulinemia were achieved (group III). When insulin was administered, we observed a significant ($p<0.001$) and stepwise increase in plasma insulin concentration depending on the dose. By simultaneous glucose infusion we produced a state of euglycemia or hyperglycemia in association with this hyperinsulinemic state. With a slight increase in plasma insulin ($61 \mu U/ml$) (group IV), we produced a significant ($p<0.001$) reduction in gluconeogenesis with a slight but not significant reduction in the rate of glucose production. With moderate to marked hyperinsulinemia (236 and 481 $\mu U/ml$, groups V and VI), there was significant ($p<0.001$) reduction of both gluconeogenesis and the rate of glucose production with either hypoglycemia (group V) or euglycemia (group IV). Insulin is known to inhibit glycogenolysis and gluconeogenesis while enhancing glycogenesis. This results in the suppression of the rate of glucose production in the adult. Our data suggested that a moderate elevation of plasma insulin level was achieved (groups II, V, and VI). It is apparent that hepatic insensitivity for insulin in the term sheep is of critical importance developmentally for glucose homeostasis (11).

Thus far in the human, limited studies of glucose kinetics have appeared that focus on the sensitivity (developmental maturation) of the newborn liver and provide quantitative data concerning the steady state hepatic glucose output and/or peripheral utilization. Perinatal glucose homeostasis includes evaluation of potentially opposing or synergistic hormonal, neural, and enzymatic systems. These biochemical and physiological controls have only been initially studied in detail in the term and preterm infant after birth during the phase of transition to mature control.

Thus far we have considered factors that indicate differences in glucose homeostasis of newborn and preterm infants compared with older infants or adults. Are these differences sufficient to account for neonatal disequilibrium of glucose metabolism?

The extremes of hyper- and hypoglycemia are observed with a higher frequency in preterm infants than in term newborns. Hyperglycemia has been reported in two siblings with a rudimentary pancreas and undetectable circulating immunoreactive insulin. This, however, is an exceedingly rare occurrence. More commonly, transient neonatal diabetes mellitus has been observed in the first 6 weeks of life in infants who are small for gestational age. Failure to thrive and severe dehydration have been noted even though an adequate intake has been documented. Extreme hyperglycemia in the absence of ketosis or acidosis is usually present. Insulin treatment with a correction of hyperglycemia produces a dramatic response. A transient deficiency in insulin secretion appears to be the basis for this disorder.

A more common occurrence is the hyperglycemia observed in very low birth weight infants. This has been documented in infants who require parenteral ali-
Glucose concentrations exceeding 300 mg/dl have been reported in infants treated parenterally within the first 24 hr of birth (12).

When low-birth-weight infants are given a large glucose load to meet caloric requirements, hyperglycemia may occur and theoretically result in glucosuria, osmotic diuresis, weight loss, and dehydration. The incidence has been reported to be as high as 43% to 86%. Although the pathogenesis is unclear, it is likely to involve multiple factors, including diminished mass of insulin-sensitive tissues, i.e., adipose tissue and muscle mass, as well as diminished insulin secretion and/or diminished or altered receptor and postreceptor action. The question of the role of insulin administration to such infants is unresolved. Insulin has been shown to be effective. In the study of Pollak et al. (13) (Fig. 4), 8 appropriate for gestational age (AGA) well infants of birth weight 1,090 ± 90 g (mean ± SEM) with a gestational age of 29 ± 0.8 weeks were given glucose infusions of 14 mg kg\(^{-1}\) min\(^{-1}\) on successive days for 4 hr. On one day a placebo infusion of saline was given for 50 min, whereas on the other day regular insulin was given for 50 min at the rate

![Graph](image.png)

**FIG. 4.** Effects of exogenous insulin on serum glucose level, serum insulin level, and insulin/glucose ratio during steady-state hyperglycemia. Single asterisk indicates that difference to baseline is significant (p < 0.05). Double asterisks indicate that statistical analysis was not done because of small numbers. (From Pollak et al., ref. 13.)
of 10 mU/kg/min. This resulted in an insulin-to-glucose ratio of 1 U per 1.4 g of glucose. The glucose infusion resulted in hyperglycemia with a rise from basal levels of 118 ±0.3 mg/dl to 169 ±13 at 60 min and 183 ±24 mg/dl at 240 min. The high basal levels were attributed to prior glucose administration. The administration of insulin resulted in a decline in glucose levels to 126 ±24 mg/dl at 180 min and to 108 ±23 mg/dl at 240 min. These levels were comparable to basal levels. Although there was a progressive rise in plasma insulin in those infants receiving only glucose, this was insufficient to restore normoglycemia. The insulin-to-glucose ratio remained low. In contrast, in the infants infused with insulin there was a rise in plasma insulin from 25.1 ±3.9 μU/ml to 275 ±47.9 μU/ml at 150 min and 90.5 ±21.2 μU/ml at 240 min. The latter levels resulted in significant increases in the insulin-to-glucose ratio from 0.22 ±0.03 basal to 1.74 ±0.35 at 150 min (p<0.001). The mechanisms operative in such infants to develop hyperglycemia are as yet not well defined in terms of hepatic versus peripheral tissue insulin responsiveness. If the response of these infants is similar to that of the newborn lambs, then increased insulin levels may be required to achieve normoglycemia in the presence of a large glucose load.

Although insulin administration has been advocated to treat hyperglycemia in young infants, there are inadequate data to support this recommendation. In the very small premature infant, the primary requirement is for sufficient nutrients to meet specific energy needs including growth. Isolated storage of glucose as glycogen or fat is not commensurate with growth, which requires DNA, RNA, and protein synthesis. Is the conversion of exogenous glucose to glycogen and lipid an advantage in the absence of other events? Administration of insulin may appear attractive to maintain normoglycemia during dextrose infusion; however, theoretical considerations and practical limitations mandate restricting its use to investigate studies at the present time.

The metabolic alterations associated with severe malnutrition have been studied extensively in five infants 12 to 22 months of age by Kerr and associates (14,15). They studied the infants when they were malnourished and again after recovery using a variety of techniques including balance studies, oxygen consumption, and kinetic estimates of glucose production with uniformly labeled D-[U-13C]glucose. Following 3 days of a standard maintenance intake of energy and protein, the infants were fasted until glycogen oxidation became negligible. Total energy utilization was significantly less in the malnourished compared with the recovered state (66 vs 79 kcal/kg/day); however, there was no significant change with fasting. There was a major shift in energy source from oxidation of dietary carbohydrate and glycogen to oxidation of fat so that by 21 hr of fasting, the malnourished subjects utilized fat for 94% of energy requirement whereas the recovered infants utilized 92% of fat after 27 hr. Utilization of protein remained low in the malnourished infants, accounting for only 4% of energy requirements, but was doubled to 7% in the recovered infants.

Plasma glucose concentration decreased to about 40 mg/dl in both groups as glycogen oxidation diminished. The maximal amount of glucose that could have
been derived from dietary carbohydrate, glycogen, glycerol and amino acids decreased during the fast from about 6 to 1 mg kg\(^{-1}\) min\(^{-1}\). Plasma alanine decreased similarly in both groups. Plasma insulin decreased to low levels in both groups. Plasma glycerol, free fatty acids, beta-hydroxybutyrate, and acetoacetate increased in both groups, but the latter three were less elevated in the malnourished subjects.

The kinetic studies with [U-\(^{13}\)C] glucose indicated that total fasting glucose production averaged 2.8 mg kg\(^{-1}\) min\(^{-1}\) (range 1.9–4.1) in the malnourished infants, and 2.7 mg kg\(^{-1}\) min\(^{-1}\) in the recovered state. Plasma glucose declined to similar levels as glycogen was utilized, reaching values of 37 mg/dl in the malnourished and 42 mg/dl in the recovered state. Oxidation of glycogen could only account for 7% of glucose production in either state. Glycerol available from fat oxidation could have accounted for 18% of glucose production in the malnourished subjects, but 22% after recovery. Available gluconeogenic amino acids could have contributed 9% and 21% of total glucose production, respectively. The remaining major source of glucose is likely to have been lactate, pyruvate, and alanine recycled via the Cori cycle.

In order to evaluate gluconeogenesis from amino acids, alanine was infused intravenously for 3 hr at 4 mg kg\(^{-1}\) min\(^{-1}\) while labeled glucose was infused continuously. There was a 15-fold increase in plasma alanine associated with an initial increase in glucose concentration and an estimated initial rate of increase of the glucose pool of 1 mg kg\(^{-1}\) min\(^{-1}\). The average final increase in plasma glucose concentration was 30 mg/dl. There were no differences in response in the malnourished compared with the recovered state. It was concluded that following glycogenolysis, the major source of gluconeogenesis in these fasting infants was recycled products of glycolysis. Because amino acids accounted for a relatively small fraction of total gluconeogenesis, the large decrease in availability of gluconeogenic amino acids associated with severe malnutrition did not result in significantly decreased glucose production or hypoglycemia. The initial increase in glucose concentration after infusion of alanine was not consistently owing to increased gluconeogenesis. The relatively small increase in the rate of glucose production after increasing alanine and the similarity between the two groups indicate that the maximal possible rate of gluconeogenesis was not much greater than the availability of endogenous substrates (14,15).

Cowett et al. (16) (Fig. 5) have evaluated glucose kinetics in glucose-infused small for gestational age (SGA) infants with uniformly labeled D-[6-\(^{13}\)C]glucose. There were 9 SGA, 7 AGA term, and 13 AGA premature infants studied at 26 ± 6, 35 ± 7, and 41 ± 8 hr of age, receiving exogenous glucose at rates of 5.7 ± 0.3 to 6.0 ± 0.4 mg kg\(^{-1}\) min\(^{-1}\). All infants were normoglycemic and had similar plasma insulin and plasma glucagon concentrations. There was considerable variation in the hepatic response to exogenous glucose. Appropriate suppression of glucose production was found in 8 of 9 SGA infants and 5 of 7 AGA term, but in only 8 of 13 AGA preterm infants. Total available glucose was significantly elevated in 1 SGA, 1 AGA term, and 5 AGA preterm infants such that rates ranged from 6.9 to 10.7 mg kg\(^{-1}\) min\(^{-1}\). It is striking that these differences were greater in the
more immature infants. Since plasma insulin and glucagon concentrations were similar, it is likely that these differences are related to some intrinsic response of the immature hepatocyte. We have previously speculated that this may be attributed to diminished hepatic responsiveness to insulin (10).

**SUMMARY**

It is apparent from the foregoing that very young infants may be at risk for disequilibrium of glucose metabolism. Both hyper- and hypoglycemia may occur during medical intervention. (An extensive discussion of hypoglycemia has not been presented, but may be found in refs. 4 and 17.) Maturation of hepatic control appears to be the primary factor in achieving glucose homeostasis.

**ACKNOWLEDGMENTS**

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REFERENCES


DISCUSSION

Dr. Tsang: I have a basic question about dose administration of any stimulus in a study of neonatal animals, especially when we are trying to draw comparisons between the neonate and, let us say, the adult. For example, in looking at the effect of glucagon administration, we see that even within the neonatal period, there are differences depending on the dose. How do we really know that a dose of 30 mg/kg given to a baby compared with 30 mg/kg given to an adult is really the same thing? What about levels of glucagon in the blood? What other factors could affect them? We often talk about differences in response between neonates and adults, but is the information on which these interpretations are based really valid?

Dr. Schwartz: It is a question of whether you want to look at the overall picture or you want a fine tune? You are now asking us to fine tune our discussion. The original studies
were carried out at a time when we were really trying to define whether there were any
differences between babies and adults, and I think we demonstrated that there were. In fact,
there is a whole body of literature regarding what is the appropriate reference standard for
anything, whether it be a drug, a nutrient, or anything else. Max Kleiber, who is a very
famous physiologist at the University of California, Davis, in his book entitled *The Fire of
Life*, devoted an entire chapter to metabolism and metabolic reference standards, i.e., how
you can compare a mouse with an elephant. The reference standard that most people use,
when we are talking about energy metabolism, turns out to be weight to the 3/4 power;
some people use weight to the 2/3 power. So, the first level of fine tuning would be to find
what that common reference standard is, for whatever parameters you are looking at: rénal
function, cardiac function, etc. I currently use weight to the 3/4 power in comparing some
studies that we are currently working on in which we are interested in comparing adults
with newborns. However, I do not think that is going to answer your question. Pharmacolo-
gists can probably answer better than I because I think you are interested in knowledge
about intimate metabolism of every single drug, and I am not even sure that measuring a
glucagon level, for example, is going to answer your question because it really relates to
how glucagon reacts with its receptor and what happens to the postreceptor events, while
we are looking 10 steps down the line at the peripheral glucose, which has 20 other things
affecting it. It is a very important issue, but it is still very complex.

**Dr. Priolisi:** Are insulin and glucagon receptor sites involved in the different patterns of
response regarding glucose production rate, among light-for-date, preterm, and full-term
babies and adults?

**Dr. Schwartz:** There are a lot of data in this area related to adults and mature animals,
but very little to babies. In cord blood monocytes and erythrocytes from normal infants and
infants of diabetic mothers, the number and affinity of insulin receptors is increased,
even in infants of diabetic mothers, when there should be so-called down régulation, if you
want to use that term, which just means that you have receptors that are just not there to
react to insulin. Of course to study insulin receptors on monocytes, you need 50 cc of
blood, which means the only opportunity is with cord blood; erythrocytes, even though
they have the receptors, at least the insulin receptors, still need a fairly large sample. It is
going to be a while until technology is sufficiently developed to permit us to answer this
kind of important question. At the moment the whole question of the hormone-receptor
interaction and the postreceptor events, as far as development is concerned, is unexplored
and undefined.

**Dr. Marini:** Dr. Tsang questioned dosage; I am questioning route of administration of
glucose. Will glucose not have different effects depending on whether it is administered
through the umbilical vein, through a peripheral vein, or by mouth?

**Dr. Schwartz:** Yes, you are absolutely right. When you give glucose by peripheral vein,
obviously it reaches the beta cell through the celiac artery and then presumably an effect is
obtained directly from glucose stimulating the beta cell. When you give glucose by the
umbilical vein, if it is prehepatic rather than posthepatic, then you have the possibility that
glucose is already having an effect, by autoregulation of the liver, i.e., the liver is respond-
ing to glucose independently from hormones, and then acts as if it was going to the periph-
ery, to the beta cell. When it is administered by mouth, you, of course, introduce all the
hormones that are so critical in understanding pancreatic release of insulin, as shown by
the work of Ainsley-Green. So, there is a body of information, and there are certainly dif-
ferences because of that. You are right, we have to be cautious.

**Dr. Marini:** You discuss glucose production by the liver and how exogenous glucose
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suppresses glucose production. What happens when you use a more physiological blend of sugars, for example, half glucose, half galactose, much closer to what the infant gets in the first months of life? Is galactose more easily metabolized by the liver cells?

Dr. Schwartz: Other than work carried out on puppies, I do not know of any data on the different effects of galactose and glucose. It is a very important subject, and the techniques that we are using lend themselves to answer that question but, as yet, we have not done so.

Dr. Stern: In that connection, it is surprising that, even though galactosemia is a very specific disease, and people have been interested in aberrations of the hormones involved in the disease, there is not more information about the natural maturation of either the 1 or the 1-6 enzyme system. Is galactose metabolizable to anything other than glucose?

Dr. Schwartz: Galactose goes to galactose-1-phosphate, then reacts with UDPG and gets converted to glucose-1-phosphate and after that it might as well be glucose. However, there are some side reactions so that an infant, for example, who is on a totally galactose-free diet can still synthesize enough galactose to make galactolipids, which are necessary for certain complex brain cerebrosides, etc. It is therefore a little more complex than that.

Dr. Rubaltelli: First, I should like to refer to some papers on the use of galactose with glucose in preterm parenteral nutrition (1,2). It seems that there are some advantages in utilizing galactose as regards insulin production. Currently, people interested in total parenteral nutrition are thinking of using maltose as a carbohydrate for intravenous use although data on the utilization of disaccharide in parenteral nutrition are very scarce. Now, what about insulin in the neonatal period; it is in fact not used because of its unpredictable effects in the preterm and in full-term babies. Could this have something to do with the peripheral receptors for insulin?

Dr. Schwartz: I agree with you completely. Just as infants are unpredictable in terms of whether they will shut off their livers in response to exogenous glucose, they are equally unpredictable in terms of response to intravenous insulin, in trying to bring a hyperglycemic state, for example, down to a normal glycemic state. This still remains an area for scientific research and not everyday care in neonatal nurseries. If one has a laboratory, one can monitor glucose every 15 min and give it intravenously in such a manner that it can be stopped instantaneously so as to avoid hypoglycemia. Then the decision has to be made as to what dose is going to be given; I always start with a low one and work up. There are essentially two or three studies in which insulin has been given to premature infants; one of them came out of our group. It was a very small study and it showed that in full-term babies glucose could be lowered but only under very strict control.

Dr. Marini: Many years ago (3,4), we studied the glycemic response of full-term newborns to exogenous insulin. We found a low response during the first day of life and almost a normal response after about a week.

Dr. Heim: I wonder if you have the latest data on the glycogen storage in the premature and full-term infant? We know the classical data of Shelley and Nelligan (5). They carried out autopsies and estimated glycogen stores in the liver of the premature infant to be around 11 g/kg/body weight. Did they estimate glycogen stores in muscle, and in white and brown adipose tissue?

Dr. Schwartz: Yes, they provided data on muscle over a fairly long period of gestation. It is higher than in the adult but not comparable to the liver where you get a two- or three-fold increase. Adult muscle has about 0.6 g per 100 g of muscle and they found 1.2—that order of magnitude. Regarding the premature infant, I have no idea; there is very little data.

Dr. Heim: I am really fascinated by the data that you have shown on plasma insulin,
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glucose production, and glucose utilization. What I really would like to emphasize is that if you look at the whole organism and convert these values to g/kg/body weight of glucose production and glucose utilization, and you compare it with the energy metabolism of the infant (which is what we are doing in Toronto), it turns out beautifully—that the glucose utilization increases up to 10 mg/kg/min, which is around 15 g/kg/day. The maximum we achieved was around 17 g/kg/day. At this point, you know that babies start to use all the glucose for synthesizing other substances. On the other hand, if you give a lower amount of glucose, 2.0 or 2.5, which is equal to the glucose production, the baby never oxydizes all the glucose, one-third always goes to synthetic processes. We tried to calculate where this glucose goes. According to our calculations, if we take Shelley and Nelligan’s data, about 0.7 to 0.8 g/kg can be used for glycogen synthesis but maybe a lot more; 1.2 g/kg/day for the synthesis of nonessential amino acids; the rest actually goes somewhere in the glycerol and fatty acid pool. Maybe in a few months’ or a year’s time, we will be able to interpret these data as far as the whole body energy metabolism is concerned.

Dr. Schwartz: I should like to make one correction. You assumed that when glucose production in 2 mg/kg/min and insulin levels remain very low (10 μU/ml) there was no glucose utilization. This is incorrect because the brain, which is an insulin-independent tissue, is still using glucose. You have to bear that in mind.

Dr. Raïhâ: Dr. Schwartz, you mentioned the insulinogenic effect of amino acids. We showed that in both preterm and full-term infants who are artificially fed with a higher protein intake than from breast milk, you will have higher levels of the branched chain amino acids. In Stockholm, Ginsburg et al. (6) have shown that the C-peptide excretion in these babies is dramatically increased. I wonder if you would like to speculate on the possible long-term effects of this insulinogenic stimulation in the infant as far as the pancreatic function is concerned?

Dr. Schwartz: Yes, I would be happy to speculate on that. We created a very interesting model for the infant of the diabetic mother by giving insulin subcutaneously, in utero, to the rhesus monkey during the last third of gestation. Mothers are normal, and delivery was made by cesarean section. We can reproduce virtually all the effects of diabetes in pregnancy, except for congenital abnormalities, but we are talking about late in pregnancy, just giving insulin to the fetus in utero. One of the things we have been interested in is looking at the response of these baby monkeys to the in utero hyperinsulinemia that we have produced exogenously. By 2, 3, 4, and 5 months of age, there is a definite difference in their ability to secrete insulin; it is suppressed. How it happens and what is going on at this time, I cannot tell you, but as a result, I do have a question about whether there may be a disadvantage to what you are talking about. We could speculate for the rest of the day and, until we get some real data, it is very important to keep an open mind.

Dr. Vidyasagar: Why is it that glucose is less insulinogenic than amino acids and have you documented the incidence of hyperglycemia when giving a combination of glucose and amino acid solutions?

Dr. Schwartz: These are very important questions but I cannot answer either of them.

References


