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## Glucose kinetics and glucose monitoring in newborn infants

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### Summary and conclusions

Before the transition from intra-uterine to the extra-uterine environment, metabolic substrates are continuously supplied via the umbilical cord. After birth the infant after a couple of hours is supplied with enteral feeding. Until sufficient enteral feeding is taken, the newborn infant is in a catabolic state. In catabolic conditions, the endogenous energy stores, e.g. glycogen and fat, are used to meet the ongoing metabolic demands. Glucose is the most important substrate. It is the major substrate for the brain. Ketone bodies, and also possibly lactate, can be used as a substrate for the brain, however to what extent these substrates play a role in the perinatal period is unknown.

In the studies reported in this thesis, glucose kinetics were measured in newborn infants. For ethical reasons, only infants were studied who received glucose intravenously to ensure normal blood glucose concentrations. These infants were considered to be at risk to have an imbalance between glucose production and glucose consumption. The amount of glucose which was infused, was kept low. This dose was chosen to prevent a total suppression of glucose production, which may occur at higher rates. Glucose kinetics were studied with a stable isotope dilution technique. As tracer for the glucose turnover studies, [6,6  $^2\text{H}_2$ ] glucose was used, allowing calculation of the so-called, "true" endogenous glucose production, due to the fact that there is no recycling of the tracer.

The results of our studies in small-for-gestational-age (SGA) infants (chapter 4) show, the preterm SGA infants have a significant lower GPR compared to the near term SGA infants ( $1.0 \pm 0.7$  vs.  $2.3 \pm 0.5$  mg/kg.min respectively). From this study we conclude that preterm SGA infants are at highest risk to an imbalance in glucose homeostasis. Beside, the lower GPR's we find in these infants, the energy stores in the preterm SGA infants will be reduced because of a combination of shorter gestation, and the intra-uterine growth retardation, implying that in these infants

probably lipolysis and ketogenesis also will be reduced. The fact that GPR is higher in SGA infants with a higher gestational age, indicates an ongoing maturation of glycogenesis (thus both glycogenolysis and gluconeogenesis), even in case of intra-uterine growth retardation.

Infants of diabetic mothers have since long been recognized to be at risk for derangements of glucose metabolism in the neonatal period (1). In infants of diabetic mother, it is hypothesized that there is a relationship between maternal diabetes and fetal/neonatal morbidity, the so-called Pedersen hypothesis (2). This hypothesis refers to the sequence of high maternal blood glucose concentrations leading to fetal hyperinsulinism and subsequent fetal macrosomia. On the basis of the Pedersen hypothesis, it should be expected that shortly after birth infants of diabetic mothers have a low GPR and a high glucose disappearance rate, because insulin suppresses GPR and increases glucose disappearance from the pool. Our studies in infants of diabetic mothers (chapter 5), where the insulin-dependent diabetes mellitus had been tightly controlled during pregnancy, indicate that, in case of strict control of the diabetes, the perinatal metabolism seems to be qualitatively normal. While receiving a glucose infusion at a rate of 3.4 mg/kg.min (mean), the infants had a GPR of  $1.8 \pm 1.3$  mg/kg.min (mean  $\pm$  SD). In the infants we studied, neither GPR was reduced directly after birth, nor was the glucose disappearance increased. With regards to the GPR we actually found the opposite, shortly after birth the infants had the highest GPR, which decreased subsequently within a few hours. There was no relationship between GPR and infusion rate. The higher GPRs in the first postnatal hours probably is related to stimulus of GPR by glucagon and/or catecholamines which increase after birth, whereas at later postnatal age due to the glucose infusion this stimulus is reduced. From a clinical point of view, the necessity of supplying i.v. glucose to these infants has to be questioned.

The relationship between GPRs and ketone body concentrations in the infants of diabetic mothers we find, illustrate that, when maternal diabetes is strictly regulated, metabolism in their newborn infants is adequately integrated. With increasing postnatal age, we find lower GPRs and in the infants with lower GPR we

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find higher concentrations of ketone bodies. Since Bougnères et al. (3) found that ketone body concentrations in newborn infants are correlated with ketone body production, it is suggested, that at lower GPR ketone body production is higher.

Despite the fact that maternal diabetes was tightly controlled, there was a relationship between the mean third trimester blood glucose value of the mothers and the standard deviation score of birth weight. This indicates that hypothesis, also holds in diabetic mother-infant pairs where the diabetes is regulated to almost normal blood glucose levels. If the relationship between mean third trimester blood glucose values and SDS of birthweight is only present in pregnancies of diabetic women, needs to be investigated in pregnancies of non-diabetic women.

The brain is the major glucose consuming organ. In appropriately sized newborn infants, brain weight is approximately 12 % of body weight (4). In case of intra-uterine growth retardation, there is a reduction in brain weight, however the relative brain size (brain weight as percentage of body weight) is increased. Moreover, the liver weight is decreased more than the brain weight (5). Thus weight of the glucose producing organ is decreased more than the weight of the most important glucose consuming organ. There are no data on the amount of glucose consumed by the perinatal brain. Our data of glucose turnover, were obtained during steady state, indicating that the glucose disappearance rate equals the glucose appearance rate. Thus brain glucose consumption during these studies can not have exceeded the glucose disappearance rate. When the total glucose disappearance was related to the brain weight, and expressed in mg/ 100 g brain tissue per minute, a value is obtained, which we have called brain glucose availability (chapter 6). Brain glucose availability ranged from 1.85 to 7,02 mg/ 100 g brain tissue per minute. This brain glucose availability was inversely related to the relative brain size. In the infants with the highest relative brain size (up to 20 %), the lowest brain glucose availability was found. From this study we conclude that especially the SGA infants have a very low glucose availability, suggesting that intra-uterine growth retardation does not only affect glucose production rate, but also influences, or regulates, cerebral metabolism. This is emphasized by the fact that despite the low glucose availability, and thus low

glucose consumption, none of the infants exhibited any neurological symptoms which could be attributed to lack of substrate for the brain. More research, possibly with use of PET scanning, is needed to unravel how the perinatal brain adapts to this low metabolic supply.

Lactate is considered to be an important compound in the intermediate metabolism. Unlike glucose, which is produced only in the liver, lactate is produced in many organs and tissues in the body, e.g. erythrocytes and muscle, and oxidized by few organs, e.g. heart (and brain ?). Most of the lactate produced, is recycled to glucose in the liver (Cori-cycle). An attempt has been made to measure lactate turnover as described in chapter 7. In this study we found a lactate appearance rate of 3.2 mg/kg.min. By analysis of the expired gas we found that 84 % of the lactate which disappears from the pool, was oxidized. Thus it seems, that recycling of lactate back to glucose in this infant was not a major pathway of lactate. Lactate kinetics are difficult to quantify, lactate is produced at many sites, and rapidly exchanges the label with pyruvate. Also the sampling and infusion sites are important, the most reliable mode to study lactate turnover probably is with infusing the tracer in the left ventricle, and sampling for enrichment of lactate in the right ventricle (6). It is clear that such studies are not feasible in newborn infants.

It is important to monitor blood glucose concentration in infants at risk for derangements in glucose homeostasis. The most reliable technique for blood glucose measurement, is with a glucose analyzer, based on the hexokinase or on the glucose oxidase method. Such equipment is not available at the bedside however, and therefore glucose teststrips are used. The reliability of such teststrips has often been questioned. Their performance mostly is evaluated with regression analysis. For adult subjects with diabetes another technique has been proposed, the error grid analysis (7), because of the limitations of regression analysis to evaluate glucose teststrips. In chapter 8, we propose an error grid analysis for newborn infants. This neonatal error grid analysis is a method, which gives insight into the clinical value of the performance of a teststrip in newborn infants. In this analysis the glucose teststrip reading is compared to the actual blood glucose value, as measured with proper

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laboratory techniques. As is clearly shown in chapter 8, regression analysis is unsuitable to evaluate the performance of glucose teststrips in newborn infants, much more information is obtained with the neonatal error grid analysis. The evaluation of two teststrips in the neonatal intensive care, showed complete different performances of these teststrips. The zones in the grid indicate the implications of a teststrip value on medical decision making based on the teststrip value.

Recently a device has been developed to measure glucose with a probe transcutaneously (7). Measurements in newborn infants show that in each infant there is a good correlation between the glucose concentration in the dialysate and the blood glucose concentration, however there is a large interindividual variation between the concentration in the dialysate. As is outlined in chapter 7 this is probably due to a relation between skin-permeability and birth weight. Therefore, the subcutaneous measurement of glucose, either by microdialysis, or directly by a glucose sensor, offers more perspective for monitoring of blood glucose in the future. It remains to be explored how the microdialysis technique, subcutaneous and transcutaneous, can be used for tracer studies.

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