MECHANISMS OF BLOOD SUGAR REGULATION IN THE FETUS IN UTERO AND IN THE NEWBORN ANIMAL

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It may be regarded as proven that the blood sugar concentration in the child starts to fall rapidly after the first few hours of life, and reaches a minimum on the 2nd-4th day. Several hypotheses, more or less well established, have been put forward concerning the significance of this "physiological hypoglycemia" and the mechanism by which it is brought about.

We know that in the early stages of ontogenesis, the liver glycogen possesses extraordinarily high "stability." It is very probable that this property of the liver glycogen is related to the development of hypoglycemia in the first hours and days of life. However, the nature of this property of the glycogen metabolism in the liver of the intrauterine fetus and the newborn infant has not yet been studied.

In his investigations of the guinea pig fetus, Nemeth [5] showed that the accumulation of large amounts of glycogen in the liver and its high stability at the end of intrauterine development may be due to the absence of active glucose-6-phosphatase from the liver. Weber and Cantero [9] showed that on the 16th day of intrauterine development, no glucose-6-phosphatase activity could be detected in the liver of rat fetuses, while on the 19th day it was present only to a very slight degree. Within a few days, the activity of the enzyme in the liver of the newborn rats was 30-40% higher than in adult animals. In our opinion, the results of these investigations provide a basis for the understanding of one of the more important aspects of the mechanism of development of the hypoglycemia in the neonatal period.

The object of the present investigation was to study the changes in the concentration and "stability" of the liver glycogen at the end of intrauterine development and during the first hours of extrauterine life, and to compare the dynamics of these changes with the changes in the blood glucose concentration.

EXPERIMENTAL METHOD

Our experiments were carried out on rabbits. The glycogen in the tissues was determined by Van der Kleiy's method [8]; the concentration of glucose liberated during acid hydrolysis of glycogen by the method of Mendel and co-workers [2, 3], using the SF-4 spectrophotometer at a wavelength of 515 mμ; the blood glucose by the method of Somogyi and Nelson [4, 6]. The "stability" of the glycogen in the tissue was studied by incubation in a moist chamber at 37° for 1 h. The intensity of hydrolysis of glycogen during incubation was expressed as the ratio between the residual glycogen and its initial concentration, in percent. According to several workers [8, 9, 10], this value reflects the trend and the intensity of the metabolic conversions of glycogen in the tissue immediately before extraction from the animal body. In most experiments laparotomy was performed on the rabbits under novocain anesthesia, but in a series of experiments general anesthesia (hexobarbital sodium) was used. Glucose was investigated in mixed blood taken by decapitation, after which the abdomen was rapidly opened and the liver of the fetus or newborn animal extracted.

EXPERIMENTAL RESULTS

The pattern of the changes in the glycogen concentration in the liver during the last days of intrauterine development and the first hours of life was studied in 128 animals (Fig. 1). The investigation showed that the liver glycogen concentration reached a maximum during the last days of intrauterine development: on the 30th-31st day of development it was significantly higher than on the 28th-29th day. However, 1 h after birth the liver glycogen concentration was significantly lower than on the 30th-31st day of intrauterine development. Until the fourth hour of

life, the concentration was not substantially changed. Starting after the fifth hour of intrauterine development it fell significantly ($P < 0.001$), reaching infinitesimally low values after the 8th-9th hour.

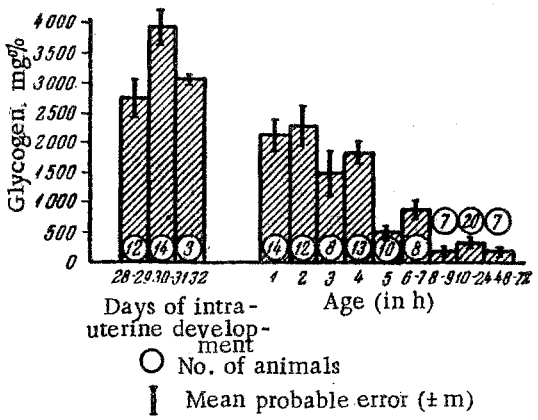

Fig. 1. Concentration of glycogen in the liver of the fetuses and newborn animals.

The trend of the changes in the blood glucose concentration of the fetuses and newborn animals was studied in 155 animals (Fig. 2). The blood of glucose concentration in the fetus reached its maximum on the 29th day of development. On the 30th-31st day it fell significantly. During the first hour of extrauterine life it showed a further fall, but during the next 4 h no substantial changes took place in the blood glucose concentration. In this period in the newborn animals, the blood sugar values were lower (below 40 mg%) than occurred in later life in physiological conditions. Starting from the fifth hour of life, a significant, although not very considerable rise in the glucose concentration in the blood was found.

If the results of the investigations illustrated in Figs 1 and 2 are compared, a remarkable coincidence is seen: the decrease in the liver glycogen concentration and the increase in the blood glucose concentration began at the same time in the early postnatal period – at the fifth hour of life. The hepatic mechanism of regulation of the blood sugar level in the first hours of life was not yet active. Its influence was observed in the rabbits only after the fifth hour of extrauterine life. We decided to find out if the appearance of the ability of the liver to hydrolyze glycogen coincided with the time of development of the blood-sugar regulating function. Experiments for the purpose of determining the time

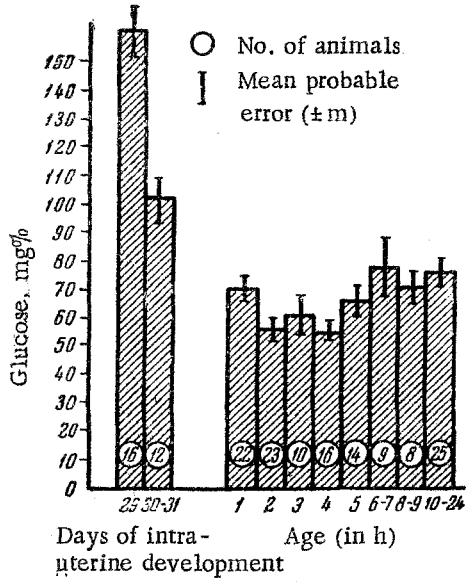

Fig. 2. Hydrolysis of glycogen during incubation of liver tissue from fetuses and newborn animals.

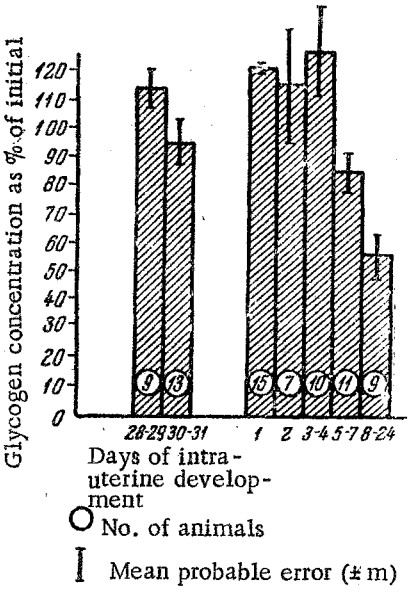

Fig. 3. Blood glucose concentration of fetuses and new born animals.

when the liver tissue began to show glycogen-hydrolyzing ability were conducted on 74 animals. The investigations of the changes in the glycogen concentration (Fig. 3) showed that in the last four days of intrauterine development and in the first 4 h of life, practically no hydrolysis of glycogen took place on incubation of the tissue; after incubation, the values found were close to the initial concentrations (about 100%). However, starting from the fifth hour of life, the incubated liver tissue showed an obvious decrease in the glycogen concentration, the intensity of which continued to increase with time. More than half the initial quantity of glycogen remained in the liver tissue taken

at the end of the first 24 h of life, after incubation. The results given in Fig. 3 show that hydrolysis of glycogen in the incubated liver tissue was first detected at the fifth hour of extrauterine life. We can therefore consider that the operation of the hepatic mechanism of regulation of the blood sugar in the neonatal period is associated with the development or the activation of enzyme systems responsible for the breakdown and utilization of the liver glycogen.

Whereas at a certain stage in the early postnatal period changes took place in the liver which could to some extent account for the changes in the glucose concentration in the blood of the newborn animals, in the intrauterine fetuses no such relationship could be demonstrated. The experiments showed that in the last days of intrauterine development a high blood glucose level was combined with a high level of "stable" glycogen in the liver. In 17 of the 22 fetuses investigated on the 28th-31st day of development, the glycogen concentration in the liver tissue was unchanged or slightly increased after incubation, and in only five animals was a slight decrease observed. It is evident that the hepatic mechanism of regulation of the blood sugar level in intrauterine development has not yet acquired the role which it assumes after a definite stage of postnatal development.

Concentration of Glucose in the Blood of the Mother Rabbit and Fetuses after Intramuscular Injection of Glucose into the Mother

Blood glucose concentration (in mg%)					
in the mother (a)	in the fetus (b)	Δ (a-b)	in the mother (a)	in the fetus (b)	Δ (a-b)
116	112	—4	257	201	—56
116	113	—3	288	223	—65
131	116	—15	300	235	—65
149	138	—11	302	220	—82
163	119	—44	305	181	—124
167	132	—35	305	260	—45
177	133	—44	306	282	—24
177	153	—24	306	183	—123
177	150	—27	311	213	—98
223	175	—48	312	254	—58
244	208	—36	313	276	—37
245	153	—92	423	223	—200
255	191	—64	551	244	—307

There are numerous reports in the literature of the active role of the placenta in regulating the fetal blood sugar. In many of these reports, however, the placenta is regarded as an organ in which glycogen can diffuse freely. This led us to carry out a series of experiments to investigate the importance of the placenta for the regulation of the blood sugar in intrauterine fetuses. Under general anesthesia, pregnant rats on the 28th-30th day of pregnancy were placed for the duration of the experiment in a bath containing physiological saline at 37-38°. A 40% solution of glucose (0.6-1.0 g glucose/kg body weight) was injected into the auricular vein of the rabbit. After various intervals of time, the fetuses were extracted in turn from the uterus, and their blood glucose concentration was determined. At the same time as each fetus was extracted, blood was taken from the auricular vein of the mother rabbit for determination of the glucose concentration. The blood glucose concentration in all the investigated fetuses was lower than that of the mother. The absolute value of the difference varied within extremely wide limits—from a few units to several hundreds of milligrams percent (see table).

Comparison of the difference (Δ) between the glucose concentrations in the blood of the mother and fetus showed that as the level of the maternal blood sugar rose the value of Δ progressively increased. The coefficient of correlation r was +0.86, indicating the presence of a positive correlation between the series of values compared ($P < 0.001$). The active role of the placenta in regulating the fetal blood sugar was quite obvious in these experiments. As the concentration of glucose in the maternal blood rose to extremely high values, the "barrier" function of the placenta in relation to the fetal blood sugar became still more marked.

The following conclusions may thus be drawn. At the end of intrauterine development, hydrolysis of glycogen in the liver of rabbit fetuses either cannot be detected or is very slight. It is evident that at this stage of ontogenesis the glycogenic function of the fetal liver as yet takes no active part in the regulation of the blood sugar level. An active role in this respect is played by the placenta.

In the early postnatal period of development of the rabbit, the glycogenic function of the liver, regulating the blood sugar level, does not become manifest immediately after birth, but only after the fifth hour of life. From this time, the mechanism of hydrolysis of glycogen begins to operate progressively in the liver, and the concentration of glycogen in the liver tissue falls rapidly. At the same time the blood glucose concentration rises. The time required for the appearance or activation of the enzyme systems carrying on the process of mobilization of the liver glycogen evidently determines to a considerable degree the duration and the depth of the hypoglycemia in the neonatal period. We do not yet possess accurate information concerning the concrete mechanism leading to the activation or development of these systems immediately after birth.

SUMMARY

A study was made of the changes in the amount and "resistance" of glycogen in the liver at the end of intrauterine development and during the first hours after birth; the dynamics of these changes is compared to the dynamic changes of blood glucose level. Experiments were staged on rabbits. Glycogen splitting in the liver of rabbits fetuses proved to be either absent or was only insignificant at the end of the intrauterine development. Evidently the liver does not taken an active part in the control of the glycemia level at this stage of ontogenesis. Glycogolysis is not active in controlling glycemia immediately after birth. The period, required for the appearance of activization of the enzyme systems in the liver, effecting the process of glycogen mobilization, largely determines the duration and the depth of hypoglycemia in the neonatal period.

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