# ANNUAL MEETING

## *European Society for Paediatric Research*

## Leuven, Belgium, September 3-6, 1979*

### HORMONAL INTERACTION AND GLUCOSE HOMEOSTASIS

M. CORNBLATH

National Institutes of Health, Bethesda, MD., USA

Throughout development,the endocrine factors involved in glucose homeostasis vary in relation to age and maturation. The endocrine-metabolic milieu in utero changes dramatically at birth and then gradually throughout infancy and childhood. The available data demonstrate a unique response of the developing infant in regulating glucose homeostasis in both health and disease. Hormone values alone, do not adequately explain the vulnerability of the neonate or infant to hypoglycemia. Additional studies involving recent advances in our understanding of hormone action through receptor sites, feed-back mechanisms and enzyme regulation will be necessary to extend our understanding of the basic mechanisms involved.

In the fetus, carbohydrate balance depends upon the maternal supply of glucose, via the placenta and, as far as is known, on fetal production of insulin and cortisol. Little data are available concerning the interactions or effects of hypothalamic factors or other hormones on fetal carbohydrate homeostasis. However, almost immediately after birth, specific, yet unique responses of multiple endocrine secretions occur. The blood glucose values tend to be lower in the neonatal period than later in the presence of normal values for cortisol, low, for insulin, and high, for glucagon, hGH, T4 and reverse T3.

The variety of hypoglycemic syndromes in the neonatal and early infancy periods elucidate some unique aspects of hormonal secretion and actions. Hyperinsulinism, in utero whether transient as in the infant of the diabetic mother, or persistent due to malformation of islet cell formation and function, can produce a number of affects before and after birth. In the primate model insulin alone has been shown to induce macrosomia, extramedullary hematopoiesis, lipogenesis and glycogen storage. There are all present in the infant of the diabetic mother, but rapidly disappear over a short period of time. In addition, increased insulin receptor sites have been demonstrated on the monocytes of cord blood of infants of diabetic mothers. However, in the infant born with an abnormality of islet cell function or formation, e.g. nesideoblastosis, the profound hypoglycemia can be life threatening even in the presence of pituitary and adrenal hormonal responses. Some data would suggest that the malformation involves not only the insulin producing beta cell, but the alpha, delta and pancreatic polypeptide cells as well and thus a total paracrine dysfunction occurs which interferes with glucose homeostasis. Preliminary data on infants with persistent hyperinsulinemia from birth and subsequently treated either operatively or with diazoxide suggest that increased insulin receptor sites may persist. Thus, the abnormality noted in hyperinsulinism may have far reaching effects beyond those usually attributed to insulin alone.

The syndrome of congenital hypopituitarism is another example of unique endocrine-glucose interrelationships in the neonatal period. This syndrome clearly indicates that the absence of growth hormone and cortisol may result in profound, even fatal, hypoglycemia in the first hours after birth. Yet, other infants with the same condition may maintain normoglycemia and later develop, ketotic hypoglycemia between 1 and 5 years of age. Hypothalamic factors have been found deficient in some of these patients leading to an inadequate feedback mechanism of carbohydrate homeostasis.

Ketotic hypoglycemia is the most prevalent form of low blood glucose between 1 and 5 years of age. Some of these were infants who had been hypoglycemic in the neonatal period as SGA babies, or because of panhypopituitarism or isolated growth hormone deficiency, while others had no previous evidence of carbohydrate intolerance. Fasting ketosis followed by hypoglycemia may reflect inadequate normal feedback mechanisms which regulate hormones responsible for glycogenolysis and gluconeogenesis. These abnormal responses disappear beyond age 7 or 8. Thereafter the child begins to show normal hormonal-glucose relationships.

Glucose homeostasis is the result of complex interactions that change profoundly throughout development. Their complex nature require the application of recently develop concepts to understand the underlying mechanisms.

### THE CONTROL OF CARBOHYDRATE METABOLISM IN THE LIVER

H.G. HERS

Laboratoire de Chimie Physiologique, Université de Louvain, and International Institute of Cellular and Molecular Pathology, Brussels, Belgium

Glucose occupies a unique position in intermediary metabolism for two reasons:

1. it is the substrate of glycolysis which is the only pathway to produce ATP in anaerobic life
2. it is the major and usually the unique substrate for brain metabolism.

The second reason is by far the most important in the human body and one major role of the liver is to maintain a normal level of glycaemia. The control of the level of glycaemia by the liver involves the storage of glucose as glycogen and the formation of glucose from endogenous source by gluconeogenesis.

#### The control of glycogen metabolism in the liver

As explained in detail in a recent review (Hers, Ann. Rev. Biochem., 45, 167-189, 1976) the rate limiting steps of glycogen synthesis and breakdown in the liver are catalyzed by glycogen synthase and glycogen phosphorylase. Each of these enzymes exist in two forms: one active (a),and the other one inactive (b). The a and b forms are interconvertible through phosphorylation by kinases and dephosphorylation by phosphatases. Glucose is readily diffusable inside of the liver cell. It binds to phosphorylase a which can be considered as the glucose receptor of the liver. The glucose bound phosphorylase a is rapidly converted to phosphorylase b by phosphorylase phosphatase. A first effect of glucose is to decrease and eventually to arrest glycogen degradation in the liver. Furthermore, phosphorylase a is a strong inhibitor of synthase phosphatase, the enzyme that activates glycogen synthase. Therefore, the disappearance of phosphorylase a as a result of glucose binding allows the activation of glycogen synthase and the initiation of glycogen synthesis. Various ionic and hormonal effects including those of insulin appear to be explained by a primary action on the inactivation of phosphorylase. Glucagon causes glycogenolysis by the intermediary of cyclic AMP, activation of protein kinase, phosphorylase kinase and phosphorylase. Each step of this glycogenolytic pathway has been observed in hepatocytes incubated in the presence of the hormones. In contrast, catecholamines and other agonists including vasopressin and angiotensin stimulate glycogenolysis by another mechanism, possibly involving a change in calcium concentration. Insulin counteracts the effect of these glycogenolytic agents by acting at various steps of the glycogenolytic cascade.

#### The control of gluconeogenesis and the futile cycles

Futile cycle is a metabolic interconversion of which the net balance is the consumption of ATP. Three such cycles exist on the pathway of glycolysis and gluconeogenesis (1) at the level of glucose/glucose 6-phosphate interconversion (2) at the level of fructose 6-phosphate/fructose diphosphate interconversion (3) at the level of pyruvate/phosphoenolpyruvate interconversion. The bestknown mechanism by which glucagon stimulates gluconeogenesis is the inactivation, by phosphorylation, of pyruvate kinase, preventing futile recycling between phosphoenolpyruvate and pyruvate. The control of the recycling between fructose 6-phosphate and fructose diphosphate is still badly understood but appears to be controlled by glucagon also. Recycling between glucose and glucose 6-phosphate occurs continuously and is controlled only by the concentration of substrate: it plays a major role in the control of glucose uptake and glucose output by the liver.

### THE TRANSPORT OF VITAMIN D

R. BOUILLON and H. VAN BAELEN

Rega Institute, University of Leuven, Leuven, Belgium

Vitamin D and its hydroxylated metabolites are transported in the blood, bound to a transport protein. For this purpose, cartilaginous fish and amphibia use lipoproteins but bony fish, reptiles, birds and mammals have a specific vitamin D-binding protein, called DBP. We have isolated DBP from the serum of man, rat and chick and compared their characteristics.