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Congenital hyperinsulinism and neonatal diabetes mellitus

Khalid Hussain

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Abstract This special edition of the Reviews in Metabolic and Endocrine Disorders provides a state of the state update on congenital hyperinsulinism and neonatal diabetes mellitus. Understanding the molecular mechanisms of these two disorders has provided fundamental insights into pancreatic beta-cell physiology. This knowledge has also had a significant impact on our clinical approach to patients with these two disorders and fundamentally changed patient management.

Keywords Glucose · Insulin · Hyperinsulinism · Diabetes mellitus

1 Introduction

Abnormalities in glucose homeostasis (hypoglycaemia and hyperglycaemia) are common in the neonatal period. Both hypoglycaemia and hyperglycaemia can occur due to many different causes in the newborn period. Hypoglycaemia may be due to prematurity, intrauterine growth retardation, maternal diabetes mellitus (gestational and insulin dependent), hormonal deficiencies (such as cortisol), a large number of metabolic conditions and dysregulated insulin secretion (as in hyperinsulinaemic hypoglycaemia). In contrast hyperglycaemia is typically observed in newborns with extreme prematurity and in neonatal diabetes mellitus (both transient and persistent).

This special edition of the Reviews in Endocrine and Metabolic Disorders focuses on providing a state of the art update on the congenital forms of hyperinsulinaemic hypoglycaemia and neonatal diabetes mellitus (both persistent and transient). Each chapter provides a clinical perspective, outlines the pathophysiology and highlights the recent advances in the field.

2 Background to hyperinsulinaemic hypoglycaemia

Hyperinsulinaemic hypoglycaemia (HH) is a cause of severe and persistent hypoglycaemia in the newborn period. Biochemically it is characterized by the inappropriate secretion of insulin in the presence of a low blood glucose concentration. Under normal physiological conditions pancreatic β-cells metabolise glucose and secrete insulin to maintain a normal (3.5–5.6 mmol/L) blood glucose concentration. In HH this coupling between glucose metabolism and insulin secretion is perturbed so that insulin secretion is uncoupled from glucose metabolism. The congenital forms of HH (congenital hyperinsulinism) lead to severe and profound hypoglycaemia in the newborn period and occur due to defects in key genes involved in regulating insulin secretion.

The delay in the diagnosis and inappropriate management of congenital hyperinsulinism is a major cause of hypoglycaemic brain injury. Significant advances have

K. Hussain (✉)
Developmental Endocrinology Research Group, Clinical and Molecular Genetics Unit, Institute of Child Health, University College London,
30 Guilford Street,
London WC1N 1EH, UK
e-mail: K.Hussain@ich.ucl.ac.uk

K. Hussain
Great Ormond Street Hospital for Children NHS Trust,
London, UK

been made in understanding the molecular basis of the congenital forms of hyperinsulinism. The most common cause of medically unresponsive congenital hyperinsulinism is inactivating mutations in the genes *ABCC8* and *KCNJ11*. Recently advances in imaging techniques such as ^{18}F-DOPA-PET/CT have radically changed the diagnostic approach to patients with diffuse and focal forms of congenital hyperinsulinism. Laparoscopic pancreatectomy (partial and near total) is now also possible for patients with congenital hyperinsulinism.

3 Background to neonatal diabetes mellitus

Neonatal diabetes mellitus (NDM) is defined as diabetes diagnosed within the first 6 months of life. It is a rare disorder that can be permanent which requiring treatment throughout life, or it can be transient, with a period of remission. Transient neonatal diabetes (TND) is defined as diabetes that starts within the first weeks of life and recovers by 18 months but patients have an increased risk of developing diabetes in later life. Over the last a few years there has been an explosion of knowledge in the field of NDM. The most common cause of isolated NDM is activating (opposite to that in congenital hyperinsulinism) mutations in the genes *KCNJ11* and *ABCC8*. More recently mutations in the insulin gene have been reported as a cause of NDM. This knowledge has not only contributed to our understanding of the pathophysiology but has also completely changed patient management. For example some patients with NDM due to mutations in the *KCNJ11* and *ABCC8* genes can now be switched from daily subcutaneous insulin injections to treatment with oral sulphonylureas.

4 Outline of the review articles

The review articles start with an update on the role of the pancreatic β-cells K_{ATP} channels in regulating insulin secretion. These channels play a key role in regulating insulin secretion. Defects in the genes *ABCC8* and *KCNJ11* (which encode the two components of the K_{ATP} channel) can lead to either HH or NDM. In the next article we highlight the recent advances in a novel imagining (^{18}F-DOPA-PET/CT) technique which has revolutionised the management of patients with congenital hyperinsulinism. The fundamental role of glutamate dehydrogenase in regulating protein induced insulin secretion is also discussed as is the role of the pancreatic glucose sensor, glucokinase in causing hyperglycaemia and hypoglycaemia. The final article on HH describes two novel causes of HH (mutations in HNF4A and HADH). The articles on NDM focus on the permanent NDM due to mutations in the *KCNJ11* and *ABCC8* and transient NDM due to over expression of *PLAGL1* and *HYMAI*. The final article in the series describes the role of insulin gene mutations leading to NDM.