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Invited review

Neuronal damage and cognitive impairment associated with hypoglycemia: An integrated view

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ABSTRACT

The aim of the present review is to offer a current perspective about the consequences of hypoglycemia and its impact on the diabetic disorder due to the increasing incidence of diabetes around the world. The main consequence of insulin treatment in type 1 diabetic patients is the occurrence of repetitive periods of hypoglycemia and even episodes of severe hypoglycemia leading to coma. In the latter, selective neuronal death is observed in brain vulnerable regions both in humans and animal models, such as the cortex and the hippocampus. Cognitive damage subsequent to hypoglycemic coma has been associated with neuronal death in the hippocampus. The mechanisms implicated in selective damage are not completely understood but many factors have been identified including excitotoxicity, oxidative stress, zinc release, PARP-1 activation and mitochondrial dysfunction. Importantly, the diabetic condition aggravates neuronal damage and cognitive failure induced by hypoglycemia. In the absence of coma prolonged and severe hypoglycemia leads to increased oxidative stress and discrete neuronal death mainly in the cerebral cortex. The mechanisms responsible for cell damage in this condition are still unknown. Recurrent moderate hypoglycemia is far more common in diabetic patients than severe hypoglycemia and currently important efforts are being done in order to elucidate the relationship between cognitive deficits and recurrent hypoglycemia in diabetics. Human studies suggest impaired performance mainly in memory and attention tasks in healthy and diabetic individuals under the hypoglycemic condition. Only scarce neuronal death has been observed under moderate repetitive hypoglycemia but studies suggest that impaired hippocampal synaptic function might be one of the causes of cognitive failure. Recent studies have also implicated altered mitochondrial function and mitochondrial oxidative stress.

Contents

Abbreviations: Et, ethidium; FJB, fluorojade-B; GR, glutathione reductase; GPx, glutathione peroxidase; MnSOD, manganese-dependent superoxide dismutase; NOX, NADPH oxidase; GSSG, oxidized glutathione; PARP-1, poly-(ADP ribose) polymerase-1; ROS, reactive oxygen species; GSH, reduced glutathione.

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1. Introduction

The brain is a dynamic organ requiring a great amount of energy. Despite it corresponds to only 2% of the total body weight, it consumes 20% of the basal body metabolic rate (Attwell and Laughlin, 2001). The main energy substrate for brain is glucose, which is transported across the blood–brain barrier by facilitated diffusion. The main glucose transporters in the central nervous system (CNS) are GLUT1 and GLUT3. GLUT1 is present in 2 isoforms, a glycosylated isoform of 55 kDa located in microvessels, and the non-glycosylated isoform of 45 kDa located in neurons, astrocytes and microglia. The high affinity glucose transporter, GLUT3, has a higher catalytic capacity and is mainly present in neurons (Simpson et al., 2007, 2008). The physiological blood glucose levels vary between 70 and 110 mg/dl (or 3.9–6.1 mM; 1 mM = 18 mg/dl) and they are strictly regulated by endocrine responses. However, fluctuations in blood glucose concentration occur as a consequence of diverse causes. The most common cause of a reduction in blood glucose levels (hypoglycemia) is the intensive use of insulin or insulin releasing drugs for the treatment of diabetic patients. The presence of an insulinoma and defective hormonal secretion of glucagon and growth hormone are also causes of hypoglycemia (Cryer et al., 2003; Tesfaye and Seaquist, 2010).

Nowadays diabetes is one of the most relevant metabolic disorders for public health due the worrying increase of diabetic cases all over the world. According to the International Diabetes Federation nowadays there are 371 million of people living with diabetes all over the world and this number is expected to increase to 552 million by 2013. Diabetes is characterized by the failure in the production or the response to endogenous insulin. There are 2 types of diabetes: type 1 diabetes is produced by the loss of β pancreatic cells, which secrete insulin whereas type 2 diabetes is the consequence of decreased insulin response (resistance) accompanied by failure of β pancreatic cells (Wrighten et al., 2009).

Moderate hypoglycemia is present when blood glucose falls to 60–40 mg/dl; in the most extreme case, severe hypoglycemia is produced when blood glucose declines below 40 mg/dl. Severe hypoglycemia can lead to coma, characterized by unconsciousness and the cessation of the electrical brain activity (flat electroencephalogram or isoelectric period), which might induce permanent neuronal damage and even death if not promptly corrected by glucose infusion (Kalimo and Olsson, 1980).

During the last decades, the intensive use of insulin or other drugs that stimulate insulin secretion as the main treatment to prevent hyperglycemia and its long-term vascular associated complications has resulted in an increase in the incidence of hypoglycemia in diabetic patients (Diabetes Control and Complications Trial (DDCT), 2006; Steil et al., 2006). Devices to continuously monitor glucose blood levels and to optimize the delivery of insulin or insulin analogues have not succeeded in completely preventing the occurrence of repeated episodes of hypoglycemia, despite their success in reducing hyperglycemia (Fatourechi et al., 2009; Yeh et al., 2012, see Section 5 in the present review). Therefore, nowadays hypoglycemia remains to be major a complication of insulin therapy.

2. Counterregulatory endocrine response to hypoglycemia

In certain conditions the brain can use other substrates to obtain energy such as lactate, pyruvate and ketone bodies, but glucose remains the main brain energy substrate (Belánger et al., 2011; Nehlig and Pereira de Vasconcelos, 1993; Shety et al., 2012; Vannucci and Vannucci, 2001 see Section 3.2). Thus, blood glucose concentrations are highly regulated by endogenous mechanisms, known as the counterregulatory endocrine response, triggered whenever hypoglycemia is present to keep blood glucose levels in the physiological range.

When blood glucose decreases below 70 mg/dl a series of mechanisms takes place in order to counterbalance glucose decline. The first response is the suppression of insulin release from β pancreatic cells when glucose concentration reaches 67 mg/dl. If glucose decreases further to 54 mg/dl the secretion of glucagon from pancreatic cells and epinephrine from the adrenal medulla is stimulated. Glucagon is a hormone produced in pancreatic cells, which increases plasma glucose levels by the stimulation of hepatic glucose production through glycogenolysis (degradation of glycogen to glucose) and gluconeogenesis (synthesis of glucose from pyruvate). Epinephrine also increases glycogenolysis and gluconeogenesis in the liver, stimulates lipolysis in adipose tissue and decreases insulin secretion while it elevates glucagon release from the pancreas. The secretion of two other hormones contributes to the counterregulatory response, growth hormone and cortisol, secreted at plasma glucose concentrations below 66 mg/dl. These hormones stimulate lipolysis in adipose tissue and ketogenesis and gluconeogenesis in the liver. The action of these hormones is slower and takes part in the response to long lasting hypoglycemia such as prolonged fasting or starvation (Beall et al., 2012; Cryer et al., 2003; Cryer, 2006; Tesfaye and Seaquist, 2010).

Two different groups of symptoms for hypoglycemia have been described. The first group includes sympathoadrenal or neurogenic symptoms, resulting from the activation of the autonomous nervous system and the release of norepinephrine and epinephrine, and includes sweating, hunger, tingling, palpitations, tremor and anxiety. These symptoms are critical for the perception of the hypoglycemic state. The neuroglycopenic symptoms (resulting from brain glucose deprivation), occur when the levels of glucose in blood fall to 2.5–3.5 mM (45–63 mg/dl) and include confusion, blurred vision, dizziness, irritability, difficulty to speak, feeling faint, drowsiness, difficulty of thinking, seizures and coma (Cryer, 2007; De Galan et al., 2006; Tesfaye and Seaquist, 2010; Warren and Frier, 2005).

It has been proposed that recurrent hypoglycemia or even one antecedent episode of hypoglycemia induces the failure of the counterregulatory hormonal response (Cryer et al., 2003; Cryer, 2006; Lin et al., 2010), leading to a vicious cycle and increasing the risk of severe hypoglycemia. In this case, the patients are unable to recognize the sympathoadrenal symptoms of hypoglycemia until the neuroglycopenic symptoms are present leading to hypoglycemia unawareness. Thus, recurrent hypoglycemia reduces the glucose levels that trigger the counterregulatory autonomic response during a subsequent hypoglycemic period. Hypoglycemia unawareness and failure in the autonomic response lead to the so-called hypoglycemia-associated autonomic failure (HAAF), which increases 25-fold or more the risk of severe hypoglycemia, which can culminate in coma, irreversible brain damage and even in the death of the patient (White et al., 1983; Cryer et al., 2003; Cryer, 2007). Clinical data suggests that about 25% of diabetic patients suffer from hypoglycemia unawareness (Geddes et al., 2008).

Hypoglycemia is recognized as a decline in blood glucose to levels below 50 mg/dl accompanied with neuroglycopenic symptoms, or below 40 mg/dl in the absence of symptoms. Severe hypoglycemia is recognized when assistance for treatment is needed (American Diabetes Association Work-group on Hypoglycemia, 2005). Hyperinsulinemia resulting from the continuous administration of insulin or insulin releasing drugs induces glucose uptake in fat, muscle and liver, inhibiting gluconeogenesis and glycogenolysis, as well as lipolysis and glucagon secretion from pancreatic cells. As a consequence, the first response to hypoglycemia (inhibition of insulin secretion) is lost and glucagon secretion suppressed. In addition, epinephrine secretion occurs at lower blood glucose levels (Beall et al., 2012).

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