REVIEW

Hexose-6-phosphate dehydrogenase: linking endocrinology and metabolism in the endoplasmic reticulum

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Abstract

Hexose-6-phosphate dehydrogenase (H6PD) got into the focus of interest due to its role in the prereceptorial activation of glucocorticoids, which has been implicated in the pathomechanism of metabolic syndrome. Genetic observations, results gained in H6PD knockout mice, and studies on differentiating adipocytes demonstrated the importance of the enzyme in metabolic regulation. A nutrient-sensing function can be postulated for the enzyme, which links metabolism to endocrinology in the endoplasmic reticulum. This review provides an overview of the recent developments concerning the enzyme and its impact on various branches of the intermediary metabolism, which make it an important subject for the research on obesity, diabetes, and metabolic syndrome.

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Introduction

The aim of the present review is to summarize the recently discovered roles of hexose-6-phosphate dehydrogenase (H6PD) in the intermediary metabolism, redox homeostasis, and signaling of the cell. Although the enzyme has been known for decades, it drew little attention until recent observations regarding its subcellular topology, tissue distribution, protein–protein interactions, and especially its role in pre-receptorial glucocorticoid activation. The novel findings have revealed that H6PD activity is an important link between the intermediary metabolism and the autocrine/paracrine effects of glucocorticoid hormones, and hence this enzyme should be considered as an intracellular nutrient sensor.

The endoplasmic reticulum (ER) as a metabolic compartment is involved in almost all important pathways of the intermediary metabolism (Csala *et al.* 2006). Accumulating evidence suggests that the ER plays a prominent role in nutrient sensing. The cells (hepatocytes, adipocytes, pancreatic β -cells, etc.) can adapt their ER capabilities to cope with the alterations of metabolic demand. Extreme metabolic conditions (either over- or undernutrition) result in ER stress sensed fundamentally by the luminal machinery of protein folding. ER stress causes the accumulation of immature proteins and triggers the unfolded protein

response (UPR) that finally leads to a variety of downstream effects, such as apoptosis, inflammation, and insulin resistance (Hotamisligil 2005, Yoshida 2007, Zhang & Kaufman 2008).

Recent observations have indicated that, besides the above signaling pathway, ER nutrient sensing can track alternative paths. Overfeeding stimulates intracellular activation of glucocorticoids in many cell types, and the concomitant autocrine and paracrine effects seem to be important elements of the pathomechanism of obesity, metabolic syndrome, and type 2 diabetes (Tomlinson *et al.* 2004, Morton & Seckl 2008). H6PD emerged as an indispensable component of the intracellular glucocorticoid activating system. The alterations of the cellular metabolic state can affect the system through the activity of H6PD that is tightly coupled to the local production of glucocorticoids from inactive precursors in the ER lumen. Therefore, H6PD can be regarded as a metabolic sensor in the ER, which connects intermediary metabolism to hormonal signaling. In accordance with the sensor function, H6PD seems to be a ubiquitous enzyme with a moderate inducibility implying that the substrate supply rather than enzyme level defines its activity. The wide distribution suggests that H6PD is also a housekeeping enzyme, playing a prosurvival role by maintaining the redox homeostasis of the ER/SR lumen. The enzymology and physiological functions of H6PD have been delineated by

excellent recent reviews (Hewitt *et al.* 2005, White *et al.* 2007, 2008); therefore, the main properties of H6PD are only briefly summarized in Table 1.

Prereceptorial glucocorticoid activation in health and disease

Glucocorticoid hormones form an important component of the homeostatic control mechanisms that, together with the immune system and autonomic nervous system, are critical in adapting to environmental challenges and thus maintain stability through change over time. Glucocorticoids regulate pathways leading to cellular proliferation, differentiation, or death, those induced (or repressed) in response to infection, tissue damage, and inflammation, pathways that maintain metabolic homeostasis and those that regulate mood and memory (Stahn *et al.* 2007). The relative expression levels of glucocorticoid receptors α and β (Lewis-Tuffin & Cidlowski 2006) as well as the intracellular level of the hormone are the principal determinants of the glucocorticoid action. Since inactive glucocorticoids constitute a major fraction in the blood, the intracellular level of the hormonally active form critically depends upon the prereceptorial activation of glucocorticoids by 11 β -hydroxysteroid dehydrogenase type 1 (HSD11B1) (Tomlinson *et al.* 2004, Morton & Seckl 2008). By converting intrinsically inert glucocorticoids (cortisone, 11-dehydrocorticosterone) into their active forms (cortisol, corticosterone), HSD11B1 increases

glucocorticoid access to receptors. Alterations of HSD11B1 expression and activity have been implicated in the pathomechanism of hypertension, type 2 diabetes, atherosclerosis, metabolic syndrome, obesity, age-related cognitive dysfunction, osteoporosis, arthritis, and many other human diseases (Stimson & Walker 2007, Chapman & Seckl 2008, Pierotti *et al.* 2008).

HSD11B1 activity is determined by the [NADPH]/[NADP⁺] ratio

HSD11B1 enzyme is an integral membrane protein of the ER with luminal active site (Ozols 1995, Mziaut *et al.* 1999, Odermatt *et al.* 1999). It catalyzes the interconversion between cortisone and cortisol using NADPH or NADP⁺ coenzyme. Although the reaction is reversible *in vitro*, the enzyme acts as a reductase *in vivo*. Due to the relatively low free enthalpy change of the reaction, the enzyme activity greatly depends on the [NADPH]/[NADP⁺] ratio in the ER lumen (Atanasov *et al.* 2004, Banhegyi *et al.* 2004, Bujalska *et al.* 2005). Although the origin, the exact composition, and the redox state of luminal pyridine nucleotides are unknown, several indirect observations show that they are separated by the membrane barrier from the cytosolic pool (Czegle *et al.* 2006, Piccirella *et al.* 2006). The redox state of the cytosolic pyridine nucleotides is determined by several oxidoreductases. By contrast, H6PD seems to be the major – if not the only – enzyme responsible for NADP⁺ reduction in the ER lumen (Hewitt *et al.* 2005). Furthermore, according to the present knowledge, the substrate supply for H6PD is ensured by a sole ER membrane protein, the glucose-6-phosphate transporter (G6PT). Thus, in the ER of hepatocyte, adipocyte, and neutrophil granulocyte (and possibly a number of other cells), HSD11B1 can be considered as a component of a complex system, which also includes H6PD and G6PT (Fig. 1). The cooperation of the three proteins is ensured by sharing a common separate pyridine nucleotide pool.

Table 1 Biochemical properties of hexose-6-phosphate dehydrogenase (H6PD)

89 kDa molecular mass	Mason <i>et al.</i> (1999) and Clarke & Mason (2003)
Human <i>H6PD</i> gene on 1p36, spanning 37 kb; five exons and four introns	Mason <i>et al.</i> (1999)
Expression in almost every organ and cell type	Hewitt <i>et al.</i> (2005)
Intraluminal positioning in the ER	Ozols (1993)
Lack of identifiable membrane-spanning region or ER retention signal	Ozols (1993)
Protein–protein interaction with HSD11B1	Atanasov <i>et al.</i> (2008)
Glucose-6-phosphate dehydrogenase plus 6-phosphoglucanolactonase activities	Collard <i>et al.</i> (1999) and Clarke & Mason (2003)
Potential substrates: glucose-6-phosphate, galactose-6-phosphate, 2-deoxyglucose-6-phosphate, glucosamine-6-phosphate, and glucose-6-sulfate	Clarke & Mason (2003)
Specificity is ensured by the glucose-6-phosphate transporter of the ER, which is selective to glucose-6-phosphate	van Schaftingen & Gerin (2002), Banhegyi <i>et al.</i> (2004) and Marcolongo <i>et al.</i> (2007)
Potential coenzymes: NADP ⁺ , NAD ⁺ , or deamino-NADP ⁺	Beutler & Morrison (1967) and Clarke & Mason (2003)
Modest inhibition by steroids and NADPH	Oka <i>et al.</i> (1981)

Figure 1 Scheme of the G6PT–H6PD–HSD11B1 triad in the ER. Glucose-6-phosphate (G6P) is transported by G6P transporter (G6PT) to the ER lumen, where it is converted to phosphoglucanate (6PG) by H6PD in a redox reaction generating NADPH. HSD11B1 utilizes NADPH as cofactor, allowing the conversion of cortisone to cortisol.

Theoretically, these circumstances can make the G6PT–H6PD–HSD11B1 system an excellent metabolic sensor of the ER. Minor changes in the $[\text{NADPH}]/[\text{NADP}^+]$ ratio in a small compartment can lead to significant alterations in glucocorticoid activation. In fact, an about tenfold excess of NADPH is required for the appropriate functioning of HSD11B1 as a reductase; a dramatic increase in the activity starts at 9:1 $[\text{NADPH}]/[\text{NADP}^+]$ ratio (Dzyakanchuk *et al.* 2008). It means that the *in vivo* set point of the NADPH–NADP⁺ redox couple is much more reduced in the ER lumen than in the cytosol (Díaz-Flores *et al.* 2006, Pollak *et al.* 2007, Panten & Rustenbeck 2008). H6PD is more resistant to feedback inhibition by NADPH than its cytosolic counterpart glucose-6-phosphate dehydrogenase (Oka *et al.* 1981), which allows the almost complete reduction of the ER luminal pyridine nucleotide pool. The redox state of luminal NADPH/NADP⁺ system is defined by cytosolic glucose-6-phosphate level with the transmission of G6PT and H6PD.

Intracellular glucose-6-phosphate concentration as a function of nutrient load

Intracellular glucose-6-phosphate concentration is a function of blood glucose and insulin levels in insulin-sensitive non-gluconeogenic tissues such as adipose tissue and skeletal muscle (Denton *et al.* 1966, Sekar *et al.* 1998). Insulin-dependent translocation of GLUT4 glucose transporter (SLC2A4) into the plasma membrane enhances glucose uptake, which results in elevated intracellular glucose-6-phosphate level. Accumulated glucose-6-phosphate fuels the G6PT–H6PD–HSD11B1 triad, which finally leads to increased prereceptorial activation of glucocorticoids (Fig. 2). In gluconeogenic tissues, intracellular glucose-6-phosphate concentration is less fluctuating; however, it can be elevated by intense gluconeogenesis in starvation (Hems & Brosnan 1971).

The system is also suitable for the indirect sensing of fatty acid levels. According to Randle's hypothesis (glucose–fatty acid cycle), free fatty acids compete with glucose for substrate oxidation. Increased free fatty acid levels lead to elevated mitochondrial $[\text{acetyl-CoA}]/[\text{CoA}]$ and $[\text{NADH}]/[\text{NAD}^+]$ ratios that inhibit pyruvate dehydrogenase activity and lead to an increase in citrate levels, which, in turn, decreases phosphofructokinase activity and hence induces an increase in glucose-6-phosphate concentration due to the inhibition of glycolysis (Randle *et al.* 1963, Randle 1998; Fig. 2).

In conclusion, overfeeding either by carbohydrates or lipids results in elevated glucose-6-phosphate level in adipose tissue and skeletal muscle. These conditions, in fact, are accompanied by enhanced glucocorticoid activation. In humans, 'whole-body' generation of cortisol by HSD11B1 increases within 2–3 h after

consumption of a mixed meal (Basu *et al.* 2006). Similarly, hyperinsulinemia and elevated free fatty acid level induce an acute increase in HSD11B1 activity in adipose tissue in humans (Wake *et al.* 2006). A very recent study has shown that luminal NADPH concentration in the ER is highly sensitive to extracellular glucose levels in HEK-293 cells expressing HSD11B1. Lowering glucose in the culture medium dose dependently decreased the reductase activity of HSD11B1 and diminished the cortisol/cortisone ratio. Coexpression with H6PD potentiated the reductase activity of HSD11B1 at high glucose concentration (Dzyakanchuk *et al.* 2008). However, the same study points out that other cell types (H4IIE liver cells and 3T3-L1 adipocytes) are less sensitive to the changes in extracellular glucose concentration. The glucose-6-phosphate availability in the ER lumen changes dramatically in two subtypes of the glycogen storage disease type 1 (GSD1). The observation that G6PT deficiency (GSD1b) significantly reduces while glucose-6-phosphatase deficiency (GSD1a) remarkably increases HSD11B1 activity strongly supports our hypothesis and proves the participation of G6PT in glucose (or glucose-6-phosphate) sensing (Walker *et al.* 2007). A complex disorder of nutrient sensing and metabolic regulation was observed in H6PD knockout mice: fasting hypoglycemia, low hepatic glycogen content, increased sensitivity to insulin, and decreased negative feedback on the hypothalamic–pituitary–adrenal axis (Lavery *et al.* 2006, 2007, Rogoff *et al.* 2007). These findings raise the important possibility that the G6PT–H6PD–HSD11B1 system plays a key role in the dynamic modifications of the acute metabolic response to feeding. The acute responsiveness suggests that the activity rather than the expression of H6PD is important in the coupling between metabolism and hormonal response.

The functioning of the system has been evidenced also in specialized endocrine cells involved in the regulation of whole-body metabolism. Local activation of glucocorticoids is required for the inhibition of glucagon secretion in the α -cells of pancreatic islets (Swali *et al.* 2008). The effect of inactive glucocorticoid precursors is abolished in H6PD-null mice or when the HSD11B1 activity is reduced with specific inhibitors (Lavery *et al.* 2006).

Pathobiochemical aspects

Beyond the physiological sensor mechanism, the G6PT–H6PD–HSD11B1 triad can participate in the pathomechanism of gluco-, lipo-, and glucolipotoxicity. Glucose and fatty acids activate the UPR and induce ER stress by an unknown mechanism. It can be supposed that the excess of reducing equivalents leads to a redox imbalance in the ER lumen with a concomitant ER stress

Figure 2 The role of the G6PT–H6PD–HSD11B1 triad in nutrient sensing of insulin-sensitive cells. Insulin stimulates the translocation of GLUT4 into the plasma membrane and hence enhances glucose uptake in muscle and adipose tissue, which results in elevated intracellular glucose-6-phosphate (G6P) level. On the other hand, high level of free fatty acids – according to Randle’s ‘glucose–fatty acid cycle’ – inhibits glucose catabolism at several key steps, most importantly at the level of the pyruvate dehydrogenase (PDH) reaction. As a consequence, glucose-6-phosphate accumulates within the cell. Accumulation of glucose-6-phosphate, in turn, fuels the G6PT–H6PD–HSD11B1 system, which leads to increased prereceptorial activation of glucocorticoids. Thus, oversupply of reducing equivalents – in the form of either carbohydrates or lipids – leads to the enhancement of glucocorticoid activation. Increasing concentrations are indicated by red arrows, and resulting enzyme inhibitions are also indicated in red. Abbreviations: FFA, free fatty acid; F6P, fructose-6-phosphate; F1,6bP, fructose-1,6-bisphosphate; Glc, glucose; G6P, glucose-6-phosphate; GR, glucocorticoid receptor; HK, hexokinase; IR, insulin receptor; MT, mitochondrion; PDH, pyruvate dehydrogenase; PFK, phosphofructokinase; Pyr, pyruvate and OAA, oxaloacetate.

(Banhegyi *et al.* 2007). On the other hand, pharmacological or genetic manipulation of the G6PT–H6PD–HSD11B1 triad leads to ER stress, UPR, and/or apoptosis in various cell types (Leuzzi *et al.* 2003, Belkaid *et al.* 2006, Kardon *et al.* 2008, Lavery *et al.* 2008) because of a deficiency in the production of reducing equivalents. The ER stress response and its effectors are activated to protect the cells from apoptosis; however, the activation of these processes under conditions of long-term elevation of free fatty acids and glucose can lead to cellular dysfunction and ultimately apoptosis. Pancreatic β -cells are especially sensitive to glulipotoxicity, perhaps not independently from their metabolic sensor function; high capacity of nutrient sensing is necessarily accompanied by a reduced protection against nutrient toxicity (Wang *et al.* 2005, Chang-Chen *et al.* 2008, Hou *et al.* 2008). However,

saturated fatty acids disrupt ER homeostasis and induce ER stress and apoptosis also in liver cells (Wei *et al.* 2006).

An additional interesting point relates to the involvement of H6PD in the formation of atherogenic hydroxysterols. Actually it has been observed that 7-ketosterols (Hult *et al.* 2004, Schweizer *et al.* 2004) and 7-keto neurosteroids (Nashev *et al.* 2007) are substrates and competitive inhibitors of HSD11B1. Potentially, the redox balance of oxysterols, determined by H6PD/HSD11B1, may be crucial in modulating glucocorticoid and oxysterol effects (Balazs *et al.* 2008, Wamil *et al.* 2008).

Taking it all-round, high nutrient (electron donor) intake in the form of either carbohydrates or lipids can lead to enhanced glucocorticoid activation, especially in insulin-sensitive, non-gluconeogenic tissues. It has been known for a long while that glucocorticoids induce a

state of insulin resistance by directly inhibiting the translocation of the GLUT4 glucose transporters to the plasma membrane and by decreased sensitivity of glycogen synthesis and glucose oxidation to insulin in skeletal muscle (Rizza *et al.* 1982, Dimitriadis *et al.* 1997). Moreover, elevated local activation of glucocorticoids stimulates preadipocyte differentiation, increases the expression of lipoprotein lipase, glycerol production, and triglyceride synthesis in visceral adipose tissue and stimulates hepatic gluconeogenesis, thereby contributing to the development of the metabolic syndrome (Bujalska *et al.* 2008, Tomlinson *et al.* 2008).

In conclusion, overnutrition (excess of reducing power) causes the elevation of intracellular glucose-6-phosphate level, which activates H6PD via G6PT. The generated and maintained high [NADPH]/[NADP⁺] ratio in the ER lumen supports glucocorticoid activation by HSD11B1. High local glucocorticoid levels counter-regulate insulin action and promote nutrient storage, hence producing the most characteristic features of the metabolic syndrome. The role of HSD11B1 in metabolism-dependent autocrine and paracrine effects is supported by growing evidence; however, the mechanism may be more general in endocrinology. Although the subcellular localization of steroid oxidoreductases has not been systematically investigated, the different preferences of the isoenzymes to reductase or dehydrogenase activity – e.g. in case of 17 β -hydroxysteroid dehydrogenase family (Luu-The 2001) – suggest that their active sites might be localized in different compartments of the cell and that the reductase activity might be due to colocalization and functional cooperation with H6PD.

Declaration of interest

The authors have nothing to disclose. The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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