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Review

Inositol phosphoglycans and preeclampsia: from bench to bedside

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ABSTRACT

The metabolic syndrome that occurs in preeclampsia reflects the complex interactions between immunological alterations and the systemic inflammation that have been shown to take place during this complication of human pregnancy. Inositol phosphoglycans play a definite role in the insulin resistance in preeclampsia with a higher production and urinary excretion of this molecule before and during preeclampsia. Recent researches suggest that the feto-placental glucose metabolism in the first and early second trimester is mainly linked to the nonoxidative pathway of glycogen catabolism supporting the pivotal role of the inositol phosphoglycan P-type. In this article we present the results of a case–control study carried out in the first trimester to evaluate the potential of urinary P-IPG release as a early marker of the disease. A single mid-stream sample of maternal urine was collected at 11 weeks of gestation for this single centre retrospective study. Twenty-seven patients out of 331 women recruited (8.1%) went on to develop preeclampsia but no sample attained positivity. Further details about the development of the metabolic syndrome during preeclampsia were retrieved also from other studies to implement our knowledge about the pathophysiology of this syndrome and to identify biochemical aspects that could help in clinical practice.

1. Introduction

New insight into the understanding of insulin action has emerged in the past two decades from the identification and partial characterization of inositol phosphoglycan (IPG) molecules (Rademacher et al., 1994; Varela-Nieto et al., 1996). IPGs are generated in cell membranes in response to insulin and are incorporated into the cell where they activate enzymes involved in glucose and lipid metabolism. Experimental evidence suggests that IPGs are important in insulin signalling and the pathogenesis of insulin resistant states (Larner, 2002; Suzuki et al., 1994). These molecules have become the object of many studies in the recent years on human pregnancy because of their dual role: as mediators involved in the insulin resistance that develops during pregnancy (Scioscia et al., 2009b) and as a potential marker of preeclampsia (Scioscia et al., 2007a; Williams et al., 2007). We have recently published a review summarizing the key aspects of this relationship (Scioscia et al., 2009a).

In this article we focus on some novel insights that derive from new researches on IPGs and preeclampsia, a complication of human pregnancy that continues to fascinate clinicians and basic scientists mainly because of its unknown etiological mechanisms and its complex pathophysiology.

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According to recent findings, it is likely that IPG P-type may not only have a causative role in the enhancement of the systemic inflammation that occurs in preeclampsia but also a potentially key role to understand the pathophysiology of this complex disease (Rademacher et al., 2007). To better understand the final hypothesis, this article will show first some specific metabolic aspects of this molecule and then highlight some clinical findings. Here we report unpublished results of a case–control study carried out in the first trimester and analyse critically the findings of two other studies.

2. The role of inositol phosphoglycans in the glycogen metabolism

It is widely accepted that alterations in the first stages of placental implantation strongly contribute to the subsequent development of preeclampsia. Histological findings and subsequent ultrasonography alterations (abnormal uterine Doppler velocimetry) are deemed to be consequences of immunological alterations that occur in early stages at the materno-fetal interface and impair trophoblast invasion (Redman and Sargent, 2003; Redman and Sargent, 2010). However, there is emergent evidence of a key role for endometrial glands in regulating placental development before the maternal arterial supply takes over (Burton et al., 2007). The secretion of the glands represents an important source of nutrients during the first trimester (and possibly the beginning of the second trimester) as it is enriched of carbohydrates and lipids and contains growth factors that may regulate placental morphogenesis (Hempstock et al., 2004). Moreover, the concentration of polyols like inositol, fructose, mannitol are significantly higher in the intravillous fluid and in coelomic and amniotic fluids than in maternal serum demonstrating that this metabolic pathway (poorly active in adult tissues) is highly active in the human conceptus during early pregnancy while the embryo develops in a low oxygen environment (Burton et al., 2002; Jauniaux et al., 2005). All these substances certainly sustain the embryo metabolism and perhaps may modulate immune responses and trophoblast invasion at the materno-fetal interface (Burton et al., 2007). Insufficient secretory capability or abnormal glycosylation of secretory MUC1 has been associated with miscarriage in humans and in animals (Jones et al., 2010).

A particular family of IPGs, namely inositol phosphoglycan P-type (P-IPG), was shown to exert specific insulin-mimetic properties on the glycogen metabolism through the activation of protein phosphatases such as pyruvate dehydrogenase phosphatase, glycogen synthase phosphatase, and glycerol-3-phosphate acyltransferase (Varela-Nieto et al., 1996). The activation of these phosphatases plays a major role in the regulation of the disposal of glucose by oxidative metabolism via pyruvate dehydrogenase, and by the nonoxidative route of storage by glycogen synthesis, both pathways classically known to be regulated by insulin (Kunjara et al., 2008). The lipogenic and hypoglycaemic effects of P-IPG have been characterized in streptozotocin-diabetic mice (Elased et al., 2001, 2004). The key role of IPGs in the glycogen metabolism has been shown in mutant cells that are unable to synthesize IPGs: they respond to insulin as determined by tyrosine phosphorylation, but are not stimulated to elicit glycogen synthesis (Lazar et al., 1994). This may be linked to the role of glycans in promoting serine/threonine dephosphorylation of a number of key enzymes in adipocyte extracts via a mechanism requiring protein phosphatase 1, the phosphatase that regulates the activity of both glycogen synthase and phosphorylase (Lazar et al., 1994; Misek and Saltiel, 1994). Furthermore, diabetic Goto–Kakizaki rats, recognized as an animal model for insulin-resistant type II diabetes, have a defect in synthesizing or releasing functional IPGs as shown by the impaired insulin-induced activation of glycerol-3-phosphate acyltransferase by P-IPG and impaired skeletal muscle glycogen synthase activation by insulin (Villar-Palasi and Farese, 1994).

The glucose metabolism in preeclamptic placentas was investigated and a glycogen accumulation in villous syncytiotrophoblast was described (Arkwright et al., 1993). Subsequent studies demonstrated insulin resistance in preeclamptic placentas with a down-regulation of insulin signalling due to serine phosphorylation (inhibitory effect) of IRS-1 and -2 (Scioscia et al., 2006a). In that study a definite association between P-IPG and the insulin signalling pathway was also demonstrated.

3. Inositol phosphoglycans and the risk to develop preeclampsia

A strong association between P-IPG and preeclampsia was demonstrated (Paine et al., 2006; Williams et al., 2007). The initial observation of increased P-IPG content in preeclamptic placenta was reported by our group (Kunjara et al., 2000). A consistent evidence of increased release of P-IPG in maternal urine in active preeclampsia compared to normal pregnancy was shown in both retrospective and prospective studies (Paine et al., 2010; Scioscia et al., 2009b). It was postulated the production of two forms of P-IPG, the soluble and lipidic one, that are both increased during preeclampsia with a far higher production of the lipidic form compared to the soluble one (10 and 3 times higher than controls, respectively) (Scioscia et al., 2007a).

The measurement of the lipidic P-IPG in urine of preeclamptic women showed a striking difference between cases and matched controls in retrospective studies (Paine et al., 2006; Williams et al., 2007) while it was possible to demonstrate in longitudinal studies a fairly steep rise of P-IPG in urine that precedes the clinical onset of preeclampsia by doubling or tripling within a week (Paine et al., 2010; Williams et al., 2007). According to these findings the increased urinary output of lipidic P-IPG was proposed as a potential marker for preeclampsia (Williams et al., 2007) and subsequently assessed in a longitudinal prospective study (Paine et al., 2010). A good sensitivity and specificity was demonstrated (88.9% and 62.7%, respectively) with a positive likelihood ratio of 5.16. It is important to highlight that given the steep rise in urinary output of the molecule in a few days, the specificity increases significantly by assessing two consecutive samples reducing the chance of a false positive test for high readings in ELISA (Paine et al., 2010). An important observation derived from that study was that many women had sporadic episodes of increased