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P-type inositol phosphoglycans in serum and amniotic fluid in active pre-eclampsia

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Abstract

Objectives: Abnormal secretion of P-type inositol phosphoglycans (IPG-P) has been described in maternal urine of pre-eclamptic women. The aim of this study was to determine the origin of production of IPG-P. We examined the IPG-P content of maternal and fetal serum, maternal urine and amniotic fluid in both normal pregnancy and pre-eclampsia.
Design: Established extraction and bioactivity assay techniques were used to compare total IPG-P levels in serum samples, and a polyclonal-antibody-based ELISA to assay the amniotic fluid and urine samples in matched pairs of women.
Subjects: Eleven women with pre-eclampsia requiring caesarean section (subjects), 11 pregnant women requiring elective caesarean section for reasons other than pre-eclampsia (controls).
Results: Our data confirm the abnormal level of IPG-P in maternal urine during pre-eclampsia. Moreover, IPG-P levels were higher in umbilical sera than in maternal sera samples. Amniotic fluid as well as urine ELISA results were significantly higher in the pre-eclamptic group compared with normal controls. Total IPG-P bioactivity in serum did not vary between serum compartments in normal pregnancy. Uterine vein IPG-P levels were lower in pre-eclampsia when compared with normal pregnancy. A possible correlation was observed between urine and amniotic fluid levels in normal women. No correlation was observed between measured blood levels and those in urine and amniotic fluid.
Conclusions: It is hypothesized that steady state equilibrium of IPG-P in serum in normal pregnancy is disrupted in pre-eclampsia. Additionally, an abnormal IPG-P sub-fraction, detectable in urine and

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amniotic fluid, may be present and involved in the pathophysiology of the syndrome, although sites of production of this abnormal form remain unclear.

Keywords: Pre-eclampsia; Inositol phosphoglycans; IPG; Amniotic fluid; Uterine vein

1. Introduction

Pre-eclampsia is a common and well-recognized multi-system disorder of human pregnancy appearing to originate in the placenta (Roberts and Redman, 1993). It remains the second leading cause of deaths behind thromboembolic disease and, worldwide, 10% of total maternal deaths are due to pre-eclampsia/eclampsia—50,000 women each year (Duley, 1992). Kunjara et al. (2000a) reported increased levels of inositol phosphoglycan of the P-type (IPG-P) in the urine of pre-eclamptic patients and proposed that it may be involved in the pathophysiology of pre-eclampsia.

The inositol phosphoglycans (IPGs) comprise an ubiquitous family of putative carbohydrate second messengers present in many cell types and species (reviewed in Rademacher et al., 1994). IPGs are released into caveolae (Sleight et al., 2002) by the action of the enzyme glycosylphosphatidylinositol phospholipase D (GPI-PLD) (Schofield et al., 2002) on their lipidic precursors, the membrane-associated glycosylphosphatidylinositol (GPI), and therefore can potentially have both autocrine and paracrine effects. Placental GPI-PLD, necessary for production of IPG-P, is not produced by the placenta but is taken up from maternal plasma (Deborde et al., 2003). Placental microvilli have been classified as tubular caveolae (Anderson, 1998) and are therefore a potential source for placenta-derived IPG molecules which can be released and enter the maternal blood stream where they could act as systemic (paracrine) factors in addition to their role as autocrine mediators of a large number of growth factors and hormones.

The essential structure of IPG is a phospho-inositol group (chiro-inositol in the P-type, myo-inositol in the A-type) and a variable glycan moiety containing glucosamine/galactosamine (Caro et al., 1997). IPGs have been proposed to have a role in the pathogenesis of various conditions, including diabetes (Kunjara et al., 1999) and pre-eclampsia (Kunjara et al., 2000a). IPGs are important also in the regulation of leptin secretion (Kunjara et al., 2000b), which has recently been shown to be a placenta-derived hormone in humans (Masuzaki et al., 1997) and may play a role in the pathophysiology of pre-eclampsia (Mise et al., 1998).

By the end of the 1980s, the pathophysiology of pre-eclampsia has been known to be a global endothelial cell disease associated with an impaired activation of immune cells such as Th1/Th2 and NK cells (Chaouat et al., 2004, 2005) and with a systemic inflammatory response (Redman and Sargent, 2003). Since then, researchers have been searching for a so-called ‘factor X’ (Walker et al., 1994) released from the placenta into the maternal circulation, leading to the maternal symptoms of pre-eclampsia (van Beek and Peeters, 1998). IPG-P has been identified as causing several effects in common with those of factor X, including platelet activation (Bruni et al., 1991), fibroblast mitogenesis (Vasta et al., 1992)