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YOUNG INVESTIGATOR REVIEW

Endothelin-1: a key pathological factor in pre-eclampsia?

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Arjun Jain obtained a BSc in biochemistry from Imperial College London (2007). Having completed with a first class honours, he then moved to the University of Cambridge for an MPhil (2008). He stayed on in Cambridge for a PhD, working with Professor Graham Burton on the role of endothelin-1 in the induction of placental endoplasmic reticulum stress in pregnancy disorders, such as pre-eclampsia and intrauterine growth restriction. He is going to take up a position in Switzerland with Professor Christiane Albrecht to continue research on pregnancy disorders.

Abstract Endothelin (ET)-1 has been implicated in a diverse range of signalling events in a wide variety of target tissues. Given its potent vasoactive function and the prevalence of hypertension in pre-eclampsia, there has been extensive research on the role of ET-1 in this disorder. Indeed, ET-1 has been suggested to contribute to hypertension in pre-eclampsia. Recently, ET-1 has also been implicated in the induction of both oxidative stress and endoplasmic reticulum stress in pre-eclampsia; each of which has been proposed to contribute to many of the clinical manifestations of this disorder. ET-1 has been shown to activate key signalling molecules that lead to induction of these stress pathways. The use of ET-receptor antagonists could block oxidative and endoplasmic reticulum stress. Hence, further research into the role of ET-1 in pre-eclampsia may lead to the development of possible strategies to circumvent these stress pathways and the associated pathology that occurs in pre-eclampsia.

KEYWORDS: endoplasmic reticulum stress, endothelin-1, hypertension, oxidative stress, pre-eclampsia

Introduction

Pre-eclampsia is a major cause of clinical morbidity and mortality in pregnant women and prenatal infants (Roberts and Hubel, 1999), affecting between 2% and 8% of all pregnancies worldwide. It is a human pregnancy-specific disorder that adversely affects maternal vascular function and fetal intrauterine growth. The condition can also predispose the offspring to increased risk of chronic diseases, such as diabetes, cardiovascular diseases and obesity in later life (Barker, 1997; Briana and Malamitsi-Puchner, 2009) and therefore poses a major public health problem. Most cases of pre-eclampsia have an onset near term, but approximately 10% of cases have an early onset before 34 weeks of gestation (Lain and Roberts, 2002). Early-onset pre-eclampsia that requires preterm delivery has an underlying pathology that differs from, and is more severe than, that of late-onset pre-eclampsia (Moldenhauer et al., 2003).

It is now well established that one of the underlying factors in the pathophysiology of pre-eclampsia is deficient conversion of the uterine spiral arteries. The placenta is supplied by maternal spiral arteries, which undergo major

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modifications during pregnancy to accommodate the increase in uterine blood flow from 45 ml/min in the non-pregnant state to 750 ml/min at term (Burton et al., 2009). This process of modification occurs between 6 and 18 weeks of gestation, over which period the maternal spiral arteries supplying the placenta undergo physiological conversion, whereby they lose their smooth muscle and elastic coats and become transformed into dilated flaccid conduits (**Figure 1**).

Pre-eclampsia is associated with abnormal conversion of the maternal spiral arteries supplying the placenta and with subsequent placental malperfusion (Khong et al., 1986; Meekins et al., 1994). The malperfusion is thought to result in placental oxidative stress and release of a complex mix of factors, including pro-inflammatory cytokines, apoptotic debris and angiogenic regulators into the maternal circulation (Cindrova-Davies et al., 2007b). Endothelin (ET)-1 is another factor that is found to be elevated in pre-eclampsia compared with normal pregnancy. In plasma from healthy pregnant women, the concentration of ET-1 ranges from 5 to 10 pg/ml, whereas the concentration is 20—50 pg/ml in the presence of pre-eclampsia (Fiore et al., 2005).

The endothelins constitute a family of vasoactive peptides that have key physiological functions in normal tissue, acting as modulators of the vascular tone, tissue differentiation, cell proliferation, development and hormone production (Nelson et al., 2003). The family of endothelins comprises three isoforms, each of 21 amino acids (ET-1, ET-2, ET-3). ET-1 is the most abundant member of this family (Struck et al., 2005) and is synthesized and secreted by a diverse range of cells, including the syncytiotrophoblast of the placenta and endothelial cells (Malassine et al., 1993). ET-1 exerts its effects by binding to the endothelin A (ETA) and endothelin B (ETB) receptors, two highly homologous cell-surface proteins that belong to the G-protein-coupled receptor superfamily (Karet and Davenport, 1994). Upon binding to these receptors, ET-1 triggers signalling events in a wide variety of target tissues (Yanagisawa et al., 1988). This review explores the diverse roles of ET-1 in pre-eclampsia. Since its discovery in 1988, the major work on ET-1 has been on its vasoactive function. However, more recently there has also been extensive research on its involvement in various biochemical pathways. This review will outline some of the most significant findings implicating ET-1 in the pathophysiology of pre-eclampsia.

Hypertension in pre-eclampsia

Pre-eclampsia is defined by the International Society for the Study of Hypertension in Pregnancy as gestational hypertension of at least 140/90 mmHg on two separate occasions $\geq$4 h apart accompanied by significant proteinuria of at least 300 mg in a 24-hour collection of urine arising *de novo* after the 20th week of gestation (Harbison et al., 2009). Maternal endothelial cell dysfunction is a key pathology that leads to many of the clinical manifestations of pre-eclampsia, including the symptoms of hypertension and proteinuria (Redman and Sargent, 2005; Roberts et al., 1989). Endothelial dysfunction is a systemic pathological state of the endothelium that is broadly defined as an imbalance between

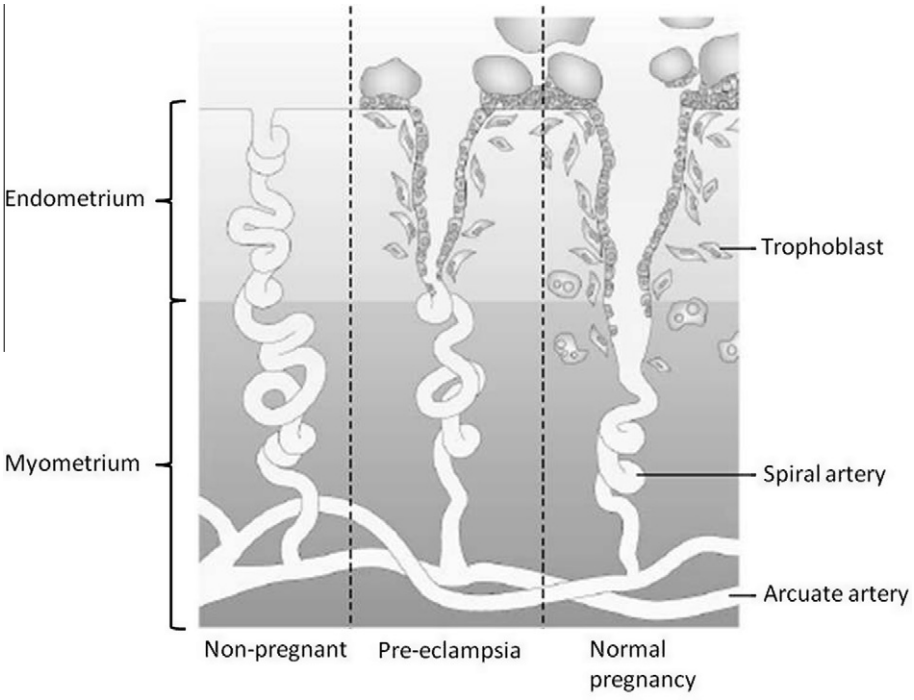

Figure 1 Schematic representation of the placenta comparing the endometrial spiral arteries in uninvaded arteries (non-pregnant), normal pregnancy and pathological conditions of pregnancy, such as pre-eclampsia. The extent and depth of trophoblast invasion is less in pathological compared with normal pregnancy, which results in inadequate transformation of the spiral arteries in the former (reproduced from Moffett-King (2002)).