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Review

Angiogenin and apoptosis in hypertension in pregnancy

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ABSTRACT

Hypertension is a common medical condition that complicates pregnancy, and has significant adverse effects on pregnancy outcomes, including maternal and perinatal morbidity and mortality. In seeking the aetiology of pregnancy-related hypertension there has been a shift in focus from the foeto-placental axis to the maternal vasculature, and two possibly related pathophysiological mechanisms have been introduced – angiogenesis and apoptosis. Both processes have been extensively studied as possible pathophysiological mechanisms underlying a variety of diseases, including cardiovascular diseases such as hypertension, myocardial infarction, as well as conditions such as malignancy states, and there is a slowly developing body of knowledge justifying hypothesis of roles in pregnancy. This review presents the data regarding this position and explores the role of angiogenesis and apoptosis in the pathogenesis of hypertension in pregnancy and their effects on pregnancy outcomes.

Introduction

With a frequency of 2–3%, hypertension is the most common medical problem encountered during pregnancy. Hypertensive disorders during pregnancy are the second leading cause, after embolism, of maternal mortality in the United States, accounting for almost 15% of such deaths. Hypertensive disorders occur in 6–8% of pregnancies and contribute significantly to stillbirths and neonatal morbidity and mortality [1,2]. The causes of most cases of hypertension during pregnancy, particularly pre-eclampsia, remain unknown, although one of the first hypotheses focused on abnormal vascular reactivity and the overproduction of vasoactive substances such as angiotensin II by the foetal/placental system [3,4]. Subsequent hypotheses predicted a role for factors such as endothelial cell activation, nitric oxide and misaligned trophoblast invasion [5–8]. More recently, it has been suggested that abnormalities in angiogenic growth factors (e.g. vascular endothelial growth factor [VEGF], angiopoietin, and more recently, angiogenin) and apoptosis may be important [9–13].

This review article aims to provide an overview of current literature and concepts relating abnormalities in angiogenesis and apoptosis and the hypertensive disorders in pregnancy. To achieve this aim we performed an on-line search of publication databases Cochrane Reviews, PubMed, MEDLINE and EMBASE, using the key words angiogenesis, apoptosis, hypertension and pregnancy. In order to identify any unpublished studies, abstracts from national (British Cardiac Society, Medical Research Society) and international (American Heart Association, American College of Cardiology, European Society of Cardiology), cardiology conferences in 2007 through 2010 were inspected. The reference lists of all papers yielded by the electronic database were scrutinised to identify any other potentially relevant articles.

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Hypertension in pregnancy

Hypertensive disorders may be classified into four categories: chronic hypertension, pre-eclampsia-eclampsia, pre-eclampsia superimposed upon chronic hypertension, and gestational hypertension. Chronic hypertension is defined as hypertension (blood pressure $\geqslant$ 140 mm Hg systolic and/or $\geqslant$90 mm Hg diastolic) that is present and observable before pregnancy or diagnosed before the 20th week of gestation. Hypertension diagnosed for the first time during pregnancy and that does not resolve postpartum is also classified as chronic hypertension. Pre-eclampsia-eclampsia is a pregnancy-specific syndrome that usually occurs after 20 weeks' gestation, or earlier in trophoblastic diseases (hydatidiform mole or hydrops). The increased blood pressure is accompanied by proteinuria in this syndrome. This can develop into full-blown pre-eclampsia, a syndrome characterised by hypertension, proteinuria and symptoms of headache, visual changes, epigastric or right upper quadrant pain and dysponea. It may be mild or severe, depending on the degree of hypertension, proteinuria and other organ system involvement, and requires treatment by specialists [1,2,14].

Angiogenesis in pregnancy

Normal intrauterine foetal development is dependent on adequate nutrient and substrate supply. Vasodilatation and development of new vessels both enable the adaptation of the uterine vasculature to the rising needs of the foetus. Angiogenesis is the process of neovascularisation from pre-existing blood vessels in response to hypoxia or substrate demands of tissues, and as such is a complex biological process comprising many steps that are precisely regulated by several molecules [15,16]. An initial step is the vasodilatation of the pre-existing vessel and formation of vesiculo-vacuolar organelles in the endothelial cells. The most important effector for this step is VEGF [17]. Subsequently, vessel destabilization and matrix degradation occur, as perivascular stroma needs to be remodelled. Angiopoietin 2 and proteases (such as chymases and matrix metallo-proteinases) are involved in this step. Endothelial cell proliferation and migration along a gradient of chemotactic agents then proceeds through the disintegrated basement membrane into the remodelled and softened perivascular space [18]. Specific mitogens of endothelial cells in this step are VEGF, angiopoietins, and fibroblast growth factor, epidermal growth factor, CXC-chemokines and insulin-like growth factor type 1, which induce the proliferation of several types of cells. This leads to lumen formation and vessel stabilization, by the migrated endothelial cells first forming a monolayer and then tube-like structures with surrounding mesenchymal cells and vascular smooth muscle cells. Different forms of VEGF and integrins have been implicated in this step [19]. In the pregnant uterus, the endometrium, decidua and placenta are sources rich of angiogenic growth factors. Angiogenic process is initiated by growth factors such as basic fibroblast growth factor (bFGF), VEGF, or placental growth factor (PlGF) [20,21]. Whilst the role of these growth factors is established, others, such as angiogenin, may also be important.

Angiogenin

Angiogenin is a member of the ribonuclease (RNase) super family. The RNases are enzymes of innate substrate specificity, but divergent functional capacities, whose distinct structure confers on angiogenin an endothelial binding motif, which it combines with its endonuclease enzyme activity and produces a potent stimulus for blood-vessel formation [22]. Physiologically, angiogenin is also induced during inflammation, exhibiting wound healing properties as well as microbiocidal activity and conferring host immunity. Markedly high levels of angiogenin can be found in the circulation without proliferative impact. Angiogenin (or RNase 5) is a 14 kDa soluble protein, first isolated from the culture medium conditioned by colon carcinoma (HT-29] cells [23]. The 123 amino acid chain and corresponding nucleotide sequences of angiogenin show 33% sequence identity and 65% homology with pancreatic RNase 1 (RNase A) [24]. The tertiary structure of angiogenin still contains many of the tertiary facets of peptide folding as seen in RNase 1, with the conservation of all key alpha helices and beta sheets [25].

Eight members have been identified in the RNase super family, and whilst each has distinct biological effects, all share a common enzymic ribonucleolytic activity on RNA [26]. In the case of angiogenin, RNase activity is directed towards 28S and 18S rRNA with the major products being 100–500 nucleotides in length [27]. Evolutionary analysis of the angiogenin lineage from non-mammalian species suggests that angiogenin and RNase 4 (closest family member to angiogenin) represent the most ancient forms of the RNase super family [28]. Recently, it has been established that angiogenin acts as an endogenous microbiocidal agent against systemic bacterial and fungal pathogens [29], extending a role for innate immunity for the rest of the RNase super family.

Angiogenin is present in plasma, in normal subjects, in a concentration of about 250–360 μg/L [28]. During human development, angiogenin has been detected in organs such as heart (in a foetus at 19 weeks), spleen (foetus at 19 and 20 weeks), lung (foetus at 19 week and adults), liver (foetus at 20 week and adult), colon, prostate, breast, brain, retina, melanocyte and foreskin (only in adults) [24,30–32]. However, angiogenesis does not take place continuously in all tissues, at all stages, as angiogenin-mediated angiogenesis requires a catalytic substrate and a cell surface receptor. Angiogenin expression is stimulated by the RNA that is likely to be released during apoptotic and necrotic cell damage in wound healing. One possible source of plasma nucleic acids that may induce RNAases is likely to relate to the phagocytotic activity of macrophages on dead cells [33], or perhaps release by apoptotic cells.

Angiogenin in pregnancy

The human placenta is one of the best in vivo models of physiological angiogenesis. Blastocyst-derived trophoblast