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Endothelin-1 receptor antagonists in fetal development and pulmonary arterial hypertension

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ABSTRACT

The Pregnancy Prevention Program (PPP) is in place to prevent drug-induced developmental malformations. Remarkably, among the ten PPP-enlisted drugs are three endothelin-1 (ET-1) receptor antagonists (ERA's: ambrisentan, bosentan and macitentan), which are approved for the treatment of Pulmonary Arterial Hypertension (PAH). This review describes the effects of ERA's in PAH pathobiology and cardiopulmonary fetal development. While ERA's hamper pathological remodeling of the pulmonary vasculature and as such exert beneficial effects in PAH, they disturb fetal development of cardiopulmonary tissues. By blocking ET-1-mediated positive inotropic effects and myocardial fetal gene induction, ERA's may affect right ventricular adaptation to the increased pulmonary vascular resistance in both the fetus and the adult PAH patient.

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1. Introduction

It is known that some medications induce severe fetal disorders when administered during pregnancy. The Pregnancy Prevention Program (PPP) was established to prevent these drug-induced developmental malformations by preventing the patient to become pregnant while using these medications. The program interdicts to start or continue a PPP-enlisted drug treatment in a pregnant patient and calls for adequate contraception in all female patients of reproductive age during treatment. Based on the patient information provided by the pharmaceutical companies, it is advised to use two forms of birth control concurrently and to perform pregnancy testing every month [1–3].

From the ten enlisted drugs in the PPP [4], three compounds are endothelin receptor antagonists (ERA's): ambrisentan, bosentan and macitentan. These ERA's are all approved for the treatment of Pulmonary Arterial Hypertension (PAH).

PAH is a progressive and devastating disease, characterized by vasoconstriction, remodeling of the pulmonary vasculature and *in situ* thrombosis [5]. These pulmonary alterations lead to an increased vascular resistance and an increase in right ventricular (RV) pressure, demanding adaptive compensatory remodeling by RV hypertrophy [5,6]. RV function is the most important prognostic determinant in pulmonary hypertension [7,8]. In addition to ERA's, 3 other classes of medication are currently approved for PAH treatment: phosphodiesterase 5 inhibitors, soluble guanylate cyclase stimulators and prostacyclin analogues [9].

The purpose of this review is to describe the role of endothelin-1 (ET-1) in embryonic and fetal development and in the pathobiology of PAH. Parallels are drawn between the teratogenic effects of ERA's in utero and their therapeutic effect in adult PAH patients.

2. Endothelin-1 and endothelin-1 receptors

Endothelin is a peptide consisting of 3 isoforms, of which ET-1 is identified as an important player in cardiovascular homeostasis through strong vasoconstricting and positive inotropic effects [10]. ET-1 also has a mitogenic effect in the vascular wall which

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is important in angiogenesis and tissue repair [11]. Although endothelial cells are the predominant source of ET-1, pulmonary arterial smooth muscle cells and lung fibroblasts are additional potential producers of ET–1 [12,13]. ET-1 responses are mediated by 2 receptor subtypes: ET-A and ET-B. Binding of ET-1 to ET-A and ET-B receptors on pulmonary artery smooth muscle cell promotes vasoconstriction, whereas activation of ET-B on pulmonary endothelial cells causes vasodilation [14] via increased endothelial secretion of prostacyclin and nitric oxide [10]. The endothelial ET-B receptor in the lungs is also responsible for the clearance of ET-1 [15,16]. ET-1 and ET-A (but not ET-B) are both expressed in the healthy RV and even more so in patients with RV hypertrophy [17]. There are two classes of ERA's: selective antagonists of either the ET-A receptor or ET-B receptor and non-selective ERA's that inhibit both receptors [10,16].

3. Endothelin-1 in embryonic and fetal development

ET-1 is important during early embryonic development. The neural crest is a transient embryonic structure unique to vertebrates that is generated at the lateral borders of the neural plate. The neural crest delaminates from the dorsal neural tube and subsets of neural crest cells migrate to various parts of the embryo, where they differentiate into a wide variety of cell types, including most of the craniofacial skeleton, cartilage, neurons and glia of the peripheral nervous system, connective tissue, neuroendocrine cells, and melanocytes (Fig. 1) [18]. The development of the neural crest is mediated by complex interactions of multiple signals and transcription factors. Bonano et al. [19], showed that early induction, migration and maintenance of neural crest specification require the ET-1/ET-A receptor signaling pathway. Thus, when endothelins and/or their receptors are affected, this will affect normal embyo-fetal development. Mice carrying targeted homozygous mutations for the ET-A receptor or ET-1 were viable to term but died shortly after birth due to severe defects in the formation of neural crest derivatives [20–22]. Malformations mainly consisted of craniofacial deformities and defects in the cardiovascular outflow tract (Fig. 1). Developmental toxicity studies with ERA's in the rat confirmed these malformations [23,24]. The pattern of fetal cardiovascular malformations is caused by the effect of ERA's on specific neural crest cells in pharyngeal arches 3, 4 and 6 that migrate to the cardiac outflow tract. These cells express ET-A receptors and are involved in maturation of the great arteries and of the outflow septation complex. The ET-1/ET-A receptor system is essential for the correct development of cardiac neural crest cells by means of an endothelium-mesenchyme interaction [22]. Also, the impaired migration of neural crest cells leads to craniofacial malformations.

In the undeveloped fetal lung, ET-1 plays an important role in the maintenance of a high vascular resistance and a low blood flow. The fetal lung endothelium regulates pulmonary artery smooth muscle cell growth and proliferation via regulation of nitric oxide, prostacyclin and ETs [25]. Levy et al., showed an increase of ET-1 expression during gestation, which was decreased after birth [26]. This is probably due to the deployment of pulmonary tissue after birth, which attenuates hypoxic pulmonary vasoconstriction. While ET-A receptor expression is strong both pre- and postnatally, expression of the ET-B receptor is low during early lung development, and increases and stabilizes in the last phases (saccular and alveolar stages) pre-natally and after birth [26]. By facilitating vasodilation and ET-1 clearance, the development of the ET-B receptor in the late fetal stage prevents muscularisation of the pulmonary pre-capillaries. ET-A receptor inhibition in the ovine fetus decreased pulmonary artery pressure, decreased right ventricular hypertrophy and attenuated the muscularization in small pulmonary arteries [27]. ET-B receptor inhibition increased pulmonary arterial pressure, increased pulmonary vascular resistance, increased right ventricular hypertrophy, increased muscularization of the small pulmonary arteries and maintained elevated ET-1 levels in the fetal lamb [28]. Indeed, impaired clearance of ET-1 in the early post-natal phase resulting in increased ET-1 plasma levels in humans is associated with Persistent Pulmonary Hypertension of the Newborn (PPHN) [25], characterized by a cardiac malformation which is caused by impaired closure of the cardiac septum resulting in a systemic-to-pulmonary shunt and high pressure in the pulmonary circulation. Animal studies showed that ET-B receptor stimulation prevents PPHN, while ET-A receptor stimulation provokes PPHN [29,30]. This might suggest that normal RV development requires an ET-1 mediated high fetal pulmonary vascular resistance. Indeed, during fetal development the RV is relatively hypertrophic and undergoes major changes from the pre-natal to post-natal phase. After birth, when the lungs deploy and the pulmonary circulation becomes uncoupled from the systemic circulation, the RV is acting as a low pressure pump. After birth, the RV shows a lower weight increase compared to the left ventricle [31], which regresses the RV hypertrophy.

4. Pulmonary arterial hypertension and the pregnancy prevention program

Pregnancy is contraindicated in female PAH patients [32], because cardiopulmonary changes during pregnancy and around delivery are associated with significant rates of disease progression and maternal death in PAH [33]. During normal pregnancy, the cardiac output increases due to a 50% increase in circulatory blood volume and an increase in heart rate of about 10–20 beats per minute [33]. To accommodate this increase in cardiac output without an increase in pulmonary artery pressure, dilatation and recruitment of additional pulmonary vessels is needed. Failure of these mechanisms is thought to be responsible for the progression of PAH during pregnancy as well as for a perceived high frequency of new PAH cases becoming manifest during pregnancy. Based on the same line of thoughts, a statement on pregnancy in PAH patients was recently published [34]. The authors of that statement advise that if possible, permanent contraception should be strongly considered and that hysteroscopic sterilization is preferred due to the lower procedural risks [34].

ERA treatment during pregnancy is also contraindicated by the PAH guideline, the PPP and the pharmaceutical companies [32,35], and ERA's are indexed as category X in the FDA pregnancy labeling categories [36]. A category X label is given when animal or human studies showed evidence of fetal risk outweighing the potential benefits of the drug [36]. When pregnancy is not terminated, treatment needs to be switched to a PDE-5 inhibitor and/or prostacyclin analogues immediately [37]. Even on treatment, PAH pregnancies are associated with high rates of premature delivery and neonatal mortality [38]. There have been no reports that the teratogenic character of ERA's found in animal studies [16,39] translates to birth defects in children of mothers with PAH using ERA's in the first days of their pregnancy.

5. Influences of endothelin-1 on the pulmonary vasculature in Pulmonary Arterial Hypertension

ET-1 is a key contributor to the pathogenesis of PAH. Higher than normal plasma and lung ET-1 levels were reported in PAH patients [10] and these increased circulating ET-1 levels correlated with PAH severity and disease prognosis [40]. ET-1, ETA, and ET-B expressions are increased in the lungs of animals with experimental pulmonary hypertension [41–43]. It has also been demonstrated that administration of ERA's in several animal models resembling

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