Final publishable summary report

Marie Curie International Reintegration Grants (IRG)

PROPOSAL „Adenosine"

Preeclampsia is a common hypertensive disorder of pregnancy, affecting 5-8% of all pregnancies. There is currently no effective cure or treatment for this disorder, aside from prompt delivery of the placenta. As such, PE is a leading global cause of maternal and infant morbidity and mortality and responsible for 76,000 deaths each year. The pathophysiology of the disease is incompletely understood and a focus of perinatal research worldwide. The most accepted hypothesis states that placental hypoxia and dysfunction lead to the release of placental substances that cause maternal endothelial dysfunction and the clinical symptoms of the disease.

Therefore, the focus of this proposal was to investigate the role of the hypoxia-inducible signal adenosine in placental development using cell culture and villous explant culture models.

Using an immortalized first trimester human trophoblast cell line HTR8/SVneo our main results show that stimulation of adenosine A_{2B} receptor reduced trophoblast migration at 2% O_2, 8% O_2 and 21% O_2 compared to untreated control cells. A_{2B} adenosine receptor stimulation decreased phosphorylation of the Mitogen Activated Protein Kinases (MAPK) ERK1/2, SAPK/JNK and p38. A_{2B} adenosine receptor activation also reduced proMMP-2 activity, MMP-2 mRNA levels and VEGF expression. These data indicate A_{2B} receptor activation blunts trophoblast migration possibly as a result of reduced activation of the MAPK signaling pathway and lower MMP-2 levels. Additional results show that hypoxia increases adenosine receptor A_{2A}, A_{2B} and HIF-1α expression of trophoblast cells, activation of the adenosine receptor A_{2B} increases the proliferation of HTR8/SVneo trophoblast cells at 2% and 8% oxygen but decreases proliferation of endothelial cells, blocking of the adenosine receptors A_{2A} or A_{2B} decreases invasion of trophoblast cells, stimulation of the A_{2B} receptor shows no effect on angiogenic activity (tubule formation) of endothelial cells.

The investigations of the effect of adenosine receptor A_{2a} and A_{2B} activation or inhibition on placental amino acid transport show no association with placental system A amino acid transporter activity. However, system A amino acid transporter activity was oxygen dependent and reduced with decreasing oxygen concentrations.

Our data suggest a role for adenosine receptor A_{2B} in placental development and possibly in the pathophysiology of preeclampsia. The identification of circulating agents, such as adenosine, that contribute to this pathology, along with their mechanisms of action, may provide a critical therapeutic target of intervention for the treatment of women at risk of developing PE. Future studies emanating from this project will further elucidate the mechanisms of adenosine action and its receptors in placental physiology.

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