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FISIOLOGIA E FARMACOLOGIA

EFEITOS DA DELEÇÃO GENÉTICA DOS GENES QUE CODIFICAM A ECA2 E O RECEPTOR MAS NA EVOLUÇÃO DA GRAVIDEZ EM CAMUNDONGOS

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BELO HORIZONTE – MINAS GERAIS

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Tese apresentada ao Programa de Pós-Graduação em Fisiologia e Farmacologia do Instituto de Ciências Biológicas da Universidade Federal de Minas Gerais como requisito à obtenção do título de Doutor em Ciências, área de concentração Fisiologia.

ORIENTADOR: PROF. DR. ROBSON AUGUSTO S. SANTOS

BELO HORIZONTE – MINAS GERAIS

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DEDICATÓRIAS

À Deus,
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RESUMO

INTRODUÇÃO: A gravidez é caracterizada por um aumento em muitos dos diferentes componentes do sistema renina-angiotensina (SRA) circulante. Durante a gravidez normal, as gestantes são normotensas graças a uma atividade aumentada do SRA. Este perfil pode ser devido, pelo menos em parte, a uma aumentada atividade do eixo ECA2 / Ang-(1-7) / MAS, o braço vasodilatador do SRA. Entretanto, não se sabe ainda se a deficiência nesse eixo vasodilatador seria uma conseqüência ou um fator contribuinte no desenvolvimento de alterações que ocorrem na gravidez.
OBJETIVO: O objetivo deste trabalho foi avaliar o efeito da deleção genética do receptor MAS ou da ECA2 no comportamento do SRA e nas alterações hemodinâmicas presentes na evolução da gravidez em camundongos.
MATERIAIS E MÉTODOS: Para avaliar diretamente essa possibilidade, alterações fenotípicas induzidas pela deficiência da ECA2 ou do MAS em camundongos C57Bl/6 e FVB/N foram determinadas na gravidez. Para isso utilizamos fêmeas C57Bl/6 ECA2$^{-/-}$, C57Bl/6 MAS $^{-/-}$, FVB/N MAS $^{-/-}$ e fêmeas controles WT, entre 12 e 20 semanas de vida, para acasalamento com machos de mesmo background e modificação genética. A pressão arterial foi mensurada por sistema de telemetria, antes e durante a gravidez, bem como até 3 dias após o parto. A função endotelial foi examinada usando a preparação de vaso isolado. O peso dos fetos e da placenta, bem como as expressões gênica placentária para componentes do SRA e protéica placentária para o receptor de VEGF foram avaliados. Também foi analisada a hemodinâmica da artéria umbilical no 19º dia gestacional, por meio de ultrassonografia, além da função renal e dos níveis circulantes de citocinas.
RESULTADOS: As fêmeas FVB/N KO MAS apresentaram uma elevação tempo-dependente da pressão arterial durante a gestação; tendência a aumentado índice de resistividade das artérias umbilicais; restrição de crescimento fetal; proteinúria; oligúria; aumento de citocinas circulantes e disfunção endotelial, características essas similares a algumas das manifestações clínicas encontradas no desenvolvimento de Pré-Eclâmpsia. Concomitantemente a esse achado, a deficiência do MAS em camundongos no background genético C57Bl/6 provocou, a princípio, níveis pressóricos normais, que se mantiveram até o final da gestação, embora sem a presença de proteinúria. No entanto, ao final da gravidez essas fêmeas apresentaram um pico pressórico, com marcante proteinúria, oligúria, aumento de citocinas circulantes, bem como disfunção endotelial e restrição de crescimento fetal, demonstrando que as conseqüências da deleção do MAS, na gravidez, é background dependente. Ainda em relação ao eixo vasodilatador do SRA, a deleção da ECA2 causou, nas fêmeas, aumentados níveis pressóricos antes da gravidez. Esse fenótipo foi mantido durante todo o período gestacional, associado, ainda, com marcante excreção fracional protéica e restrição de crescimento fetal, caracterizando alguns dos sintomas clínicos verificados no quadro de mulheres que desenvolvem a Pré-Eclâmpsia sobreposta à hipertensão arterial crônica.
CONCLUSÃO: A deleção genética de componentes do eixo vasodilatador do SRA causou ajustes hemodinâmicos alterados durante a gravidez, caracterizados, principalmente, por elevação da pressão arterial no final da gestação e restrição de crescimento fetal em camundongos. Estes dados suportam um importante papel do eixo ECA2 / Ang-(1-7) / MAS no desenvolvimento fetal e no ajuste hemodinâmico durante a gestação, sugerindo que esse eixo possa ser um importante alvo terapêutico para o tratamento de alterações existentes durante o período gestacional.

ABSTRACT

BACKGROUND: Pregnancy is characterized by an increase in many of the different components of the circulating renin-angiotensin system (RAS). During normal gestation, pregnant woman are normotensive because there is an increased activity of RAS. This could be due, at least in part, to the increased activity of the ACE2/Ang-(1-7)/Mas axis, the vasodilator arm of the RAS. However, it is not clear if the deficiency in this vasodilator axis is a consequence or contributing factor in the development of abnormalities in pregnancy.
AIM: The aim of this study was to evaluate the effect of genetic deletion of MAS receptor or ACE2 in the RAS activity and in the hemodynamic changes present in the evolution of pregnancy in mice.
MATERIALS AND METHODS: To directly investigate this possibility the phenotypic alterations induced by ACE2 or MAS deficiency in C57Bl/6 and FVB/N were determined in pregnant mice. Twelve - twenty weeks old C57Bl/6 $ACE2^{-/-}$, C57Bl/6 $MAS^{-/-}$, FVB/N $MAS^{-/-}$, and WT female mice were used for mating with males of similar background and genetic modification. Blood pressure was measured, by telemetry, before, during the pregnancy and until 3 days after delivery. The endothelial function was examined using isolated vessel preparations. The pups and placenta weight were assessed, as well as placental gene expression for RAS components and protein expression for VEGF- receptor. We also analyzed the hemodynamic of umbilical artery, on 19^{th} pregnancy day, by ultrasound, as well as a renal function and a cytokine circulating levels.
RESULTS: The female mice FVB/N MAS KO presented an increased, time-dependent, in the blood pressure levels, during the pregnancy; tendency to increased umbilical arteries resistivity index, fetal growth restriction, proteinuria, oliguria, increase in cytokines and endothelial dysfunction similar to some of the clinical manifestations found in the development of preeclampsia. Concomitantly with this finding, the deficiency in the MAS KO mice, in the genetic background C57Bl/6, resulted in the normal blood pressure levels, in the beginning, which remained until the end of pregnancy, although without the presence of proteinuria. However, in late pregnancy these females showed a pressure peak, with marked proteinuria, oliguria, increased cytokines, endothelial dysfunction, as well as a fetal growth restriction, demonstrating that the consequences of the MAS deletion, in pregnancy, is background dependent. In addition in the vasodilator axis of the RAS, the ACE2 deletion caused, in females, increased blood pressure before pregnancy. This phenotype was kept throughout the gestational period, associated, also, with striking fractional excretion of protein and fetal growth restriction, featuring some of the clinical symptoms observed in the context of women who develop preeclampsia superimposed on the chronic arterial hypertension.
CONCLUSION: The genetic deletion of the RAS-vasodilatatory axis components leads to abnormal hemodynamic adjustment during pregnancy, mainly characterized by elevated blood pressure in late pregnancy and fetal growth restriction in mice. These data support an important role of the ACE2 / Ang-(1-7) / Mas axis in the fetal development and hemodynamic adjustment during pregnancy, suggesting that this axis may be an important therapeutic target for the treatment of existing changes during pregnancy.

"A literatura deve ser realmente o lugar onde podem surgir novas idéias que repensem o mundo." (Salman Rushdie)

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