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TESE DE DOUTORADO

Avaliação de sistemas vasoativos: papel dos autoanticorpos na preeclâmpsia

Tese apresentada ao Programa de Pós-Graduação em Ciências Biológicas: Fisiologia e Farmacologia do Instituto de Ciências Biológicas da Universidade Federal de Minas Gerais para obtenção do Título de Doutor em Ciências.

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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS BIOLÓGICAS
FISIOLOGIA E FARMACOLOGIA

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RESUMO

Preeclampsia (PE) é uma das principais causas de morte maternal e o maior fator contribuinte para a morbidade maternal e perinatal. Entretanto, os mecanismos implicados nesta doença ainda são pouco compreendidos. Estudos recentes, têm demonstrado que a PE está associada com um desbalanço entre o peptídeo vasoconstritor, angiotensina II (Ang II) e o eixo vasodilatador angiotensina-(1-7)/ receptor Mas (Ang-(1-7)/receptor Mas). Além disso, a Ang-(1-7) está reduzida enquanto, a endotelina, um potente peptídeo vasoconstritor, está aumentada nas mulheres preeclâmpticas (MPEs). Somando- se a isso, os autoanticorpos maternos (AACs), capazes de se ligarem e ativar o receptor AT_1 da Ang II, estão envolvidos nessa doença. Os objetivos deste trabalho foram avaliar os sistemas vasoativos na placenta, bem como investigar a frequência e os alvos dos AACs na PE. Mulheres no terceiro trimestre de gestação foram divididos em dois grupos: preeclâmpticas (32 casos); normotensas saudáveis (29 casos). Todas as mulheres foram submetidas ao exame de Doppler e foram medidos os índices de resistência das artérias uterinas (IRU), de pulsatilidade da artéria umbilical (IP/U), da artéria cerebral- umbilical (C/U) e a incisura bilateral. A expressão protéica (face fetal da placenta) para o receptor da Ang-(1-7), Mas, enzima conversora de angiotensina 2 (ECA2), enzima conversora de angiotensina (ECA), para o receptor AT_1 da Ang II, a óxido nítrico sintase endotelial (eNOS) e para o receptor ETA da endotelina (ET-1) foram analisados por western blotting. Nas MPEs houve uma redução da expressão do Mas e da eNOS, enquanto o receptor ETA estava “regulado para cima”($p= 0.0016$; $p= 0.004$; $p= 0.002$, respectivamente). Não foram observadas diferenças significativas na expressão protéica para o receptor AT_1, ECA e ECA2 nas preeclâmpticas quando comparadas às mulheres controle. Além disso, as imunoglobulinas foram precipitadas das amostras de soro. A presença de AACs foram avaliadas em cardiomiócitos de ratos neonatos. As MPEs (97%) apresentaram AACs agonistas ao receptor AT_1 (AACs-AT_1). O efeito agonista dos AACs foi bloqueado pelo Irbesartan e neutralizado pelo peptídeo correspondente à segunda alça deste receptor. Surpreendentemente, descobrimos que 53% das MPEs apresentaram além de AACs-AT_1, um novo autoanticorpo agonista do receptor ETA (AACs-ETA). Estes foram seletivamente bloqueados pelo antagonista BQ123 e neutralizados por peptídeos correspondentes a segunda alça do receptor

ETA. Em mulheres grávidas normotensas não foram detectados AACs. Adicionalmente, o IPU mostrou-se aumentado nas MPEs ($p = 0.003$) quando comparadas às normotensas. Neste estudo, descrevemos pela primeira vez, a presença dos AACs-ETA na PE. Estes resultados sugerem que o desbalanço entre os receptores da Ang-(1-7), Mas, da endotelina ETA e a eNOS associados à presença de ambos AACs, os AACs-AT_1 e da ETA, podem estar envolvidos na patogênese da PE. Em outra etapa do trabalho, foram avaliados os efeitos cronotrópicos da Ang-(1-7) e da endotelina (ET-1) em cardiomiócitos de ratos neonatos. Por último, foi avaliada a modulação no sistema renina angiotensina (SRA) pela ET-1 na expressão protéica da ECA2 e do receptor Mas nestes miócitos. Nossos dados mostraram que a Ang-(1-7) evocou efeito cronotrópico negativo, que foi completamente abolido, pela adição do A779. Este bloqueio resultou em um aumento significativo do efeito cronotrópico positivo elicitado pela Ang II ($p<0.001$). De forma similar, os efeitos cronotrópicos positivos elicitados pelos AACs-AT_1 foram aumentados significativamente pelo bloqueio do receptor Mas com o A779 ($p<0.001$). Nossos últimos resultados, demonstraram pela primeira vez, que a ET-1 “regulou para baixo” a expressão protéica tanto da ECA2 quanto do receptor Mas em cardiomiócitos. Finalmente, a incubação dos miócitos com a ET-1, aumentou de forma significativa, o efeito cronotrópico positivo elicitado pela Ang II e reduziu o efeito cronotrópico negativo evocado pela Ang-(1-7) ($p< 0.001$). Portanto, estes resultados sugerem que existe uma modulação intrínsica entre os dois eixos antagônicos: Ang II/ ECA/AT_1 e Ang-(1-7)/ECA2/Mas. Além disso, a ET-1 modula o SRA, desviando o sistema para o eixo vasoconstrictor. Concluindo, o balanço entre estes dois eixos antagônicos, determina a direção do SRA para condições fisiológicas ou patológicas.

PALAVRAS CHAVES: preeclâmpsia, autoanticorpos agonistas do receptor AT_1 e do receptor ETA, Ang-(1-7), receptor Mas.

ABSTRACT

Preeclampsia (PE) is a leading cause of maternal death and a major contributor to maternal and perinatal morbitidy. However, the mechanisms implicated in this disease are still poorly understood. Recent studies have shown that PE is associated with a mismatch between the vasoconstrictor peptide angiotensin II (Ang II), and the vasodilator peptide angiotensin-(1-7)/receptor Mas (Ang-(1-7)/Mas) axis. Moreover, Ang-(1-7), is decreased while endothelin, a potent vasoconstrictor peptide, is elevated in preeclamptic women (PEW). Furthermore, maternal autoantibodies (AABs), capable of binding to and activating the Ang II receptor type 1 (AT_1), have also been implicated in this disease. The aims of this study were both to evaluate placental vasoactive systems and to investigate the frequency and the targets of AABs in PE. Women at third trimester of gestation were divided into two groups: preeclamptic (32 cases); normotensive healthy (29 cases). All women underwent Doppler examination of uterine arteries resistence index (uterine RI), bilateral notches, umbilical artery index (U/PI) and cerebral–umbilical artery pulsatility index (C/U). Protein expression (fetal placental tissues) for the Ang-(1-7) receptor Mas, angiotensin converting enzyme 2 (ACE2), angiotensin converting enzyme (ACE), Ang II receptor AT_1, endothelial oxid nitric sintase (eNOS) and endothelin receptor ETA were analysed by western blotting. In PEW there was a decreased expression of Mas and eNOS while ETA receptor was upregulated ($p= 0.0016$; $p= 0.004$; $p= 0.002$, respectively). No significant changes were observed for AT_1 receptor, ACE, ACE2 expression in preeclamptic ones when compared to controls. Furthermore, immunoglobulins were prepared from serum samples. The presence of AABs were assessed on cultured neonatal spontaneously beating rat cardiomyocytes. In preeclamptic patients (97%) presented AABs directed against the Ang II receptor AT_1. The agonistic effect of the the AABs was blocked by AT_1 antagonist Irbesartan and neutralized by a peptide corresponding to the second extracelular loop of this receptor. Strikingly, we discovered that 53% of the PEW's serum contained additionally to the AT_1 receptor AABs, a novel agonistic-like autoantibody, directed against the endothelin ETA receptor (ETA – AABs). It was selectively blocked by the antagonist BQ123 and also neutralized by peptides corresponding to the second extracelular loop of ETA receptor. In normotensive pregnant women no AABs were detected.

Moreover, these PEW showed increased U/PI ($p= 0.003$) compared to controls. In this study, we described for the first time, the presence of ETA-AABs in PE. Our results suggest that an imbalance of Mas/ETA receptors and eNOS associated to the presence of both agonistic AABs, against AT_1 and ETA receptors, may be involved in the pathogenesis of PE.

Furthermore, there were also evaluated the chronotropic effects of both Ang-(1-7) and endothelin (ET-1) on cultured neonatal spontaneously beating rat cardiomyocytes. At last, it was assessed the modulation of RAS by ET-1 on ACE2 and Mas receptor protein expression in these myocytes. Our data showed that, Ang-(1-7) evoked a negative chronotropic effect, which was abolished by the addition of A779, and this blockage elicited an increased positive chronotropic effect evoked by Ang II ($p<0.001$). Similarly, the positive chronotropic effects elicited by agonistic AABs against AT_1 receptor were increased by the blockage of Mas receptor with A779 ($p<0.001$). Our last results demonstrated, for the first time, that ET-1 dowregulated both ACE2 and Mas receptor protein expression ($p<0.001$) in cardiomyocytes. At last, the incubation of the myocytes with ET-1 increased the positive chronotropic effects elicited by Ang II and reduced the negative chronotropic effects evoked by Ang-(1-7) ($p< 0.001$). Therefore, these results suggest that there is an intrinsic modulation between the antagonic axis: Ang II/ ACE/AT_1 and Ang-(1-7)/ACE2/ Mas. Moreover, ET-1 modulates RAS, deviating the system to the vasoconstrictor axis. In conclusion, the balance between these antagonic axis can determinate the direction of RAS forward to either physiological or pathological conditions.

KEY WORDS: preeclampsia, autoantibodies against AT_1 and ETA receptors, Ang-(1-7), Mas receptor.

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