UNIVERSITI TEKNOLOGI MARA

THE ROLE OF ANGIOTENSIN CONVERTING ENZYME 2 AND MARINOBUFAGENIN IN LEPTIN INDUCED HYPERTENSION AND PROTEINURIA DURING PREGNANCY IN SPRAGUE DAWLEY RATS

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MSc

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the result of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate Studies at Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Leptin administration to pregnant rats increases systolic blood pressure (SBP), urinary protein excretion and markers of endothelial activation. Although the precise mechanism for this remains unclear, marinobufagenin (MBG) has been implicated in some rodent models of pregnancy related hypertension. This study therefore investigated the effect of resibufogenin (RBG), a MBG antagonist, on leptin-induced changes in blood pressure, levels and expressions of markers of endothelial activation and ACE2 and proteinuria during pregnancy in normotensive rats. Four groups of Sprague-Dawley rats (n=8), aged 12 weeks were given either normal saline (CONTROL) or 120µg kg^{-1} day^{-1} of leptin (LEP), or 120µg kg^{-1} day^{-1} of leptin+30µg kg^{-1} day^{-1} of resibufogenin (L+RBG) or 30µg kg^{-1} day^{-1} of resibufogenin (RBG) from day 1 to 20 of pregnancy. Systolic Blood pressure (SBP) was measured at Day 0 and every 5 days of pregnancy. Body weight and urinary protein excretion (UPE) were measured at Day 0 and Day 21. Animals were euthanized on Day 21 of pregnancy. Serum was collected for analysis of ACE2, VCAM-1, ICAM-1, E-selectin and endothelin-1. Kidneys and placentae were collected for histological analysis and gene expressions of ICAM-1, endothelin-1 and ACE2. Compared to the CONTROL, L+RBG and RBG groups, SBP, UPE, ICAM-1, and endothelin-1 levels in serum were significantly higher in the LEP group. ACE2 concentration in the kidney was significantly lower in the LEP group when compared to that in the CONTROL. ICAM-1 gene expression in kidney and endothelin-1 expression in placenta were significantly higher in LEP group when compared to that in the CONTROL, L+RBG, and RBG-treated rats. Endothelin-1 expression in the kidney was significantly higher in the LEP group when compared to that in CONTROL. ACE2 gene expressions in the kidney and placenta were significantly lower in the LEP group when compared to that in the CONTROL and RBG groups and RBG group respectively. No significant differences were evident in the histological analysis between the four groups. This study confirms the previously reported effects of leptin on SBP, UPE, and markers of endothelial activation and ACE2 during pregnancy in the rat. Their prevention by resibufogenin suggests that these effects on blood pressure, proteinuria, and ACE2 might be mediated via marinobufagenin. Clearly more studies are needed to further assess the role of marinobufagenin in hypertension and proteinuria of pregnancy.

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