Angiotensin II Induces Interleukin-1β–Mediated Islet Inflammation and β-Cell Dysfunction Independently of Vasoconstrictive Effects

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4378970
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Year 2015
Title Angiotensin II Induces Interleukin-1β–Mediated Islet Inflammation and β-Cell Dysfunction Independently of Vasoconstrictive Effects
Journal Diabetes
Volume 64
Number 4
Pages / **Article-Number** 1273-83
Keywords Angiotensin II/*pharmacology; Animals; Apoptosis/drug effects; Blood Glucose/metabolism; Chemokine CCL2/metabolism; Diabetes Mellitus, Type 2/metabolism; Diet, High-Fat; Humans; Inflammation/*chemically induced/metabolism; Insulin/secretion; Interleukin-1beta/*metabolism; Islets of Langerhans/*drug effects/metabolism; Mice; Mitochondria/drug effects/metabolism; Renin-Angiotensin System/physiology; Vasoconstriction/*drug effects
Mesh terms Angiotensin II, pharmacology; Animals; Apoptosis, drug effects; Blood Glucose, metabolism; Chemokine CCL2, metabolism; Diabetes Mellitus, Type 2, metabolism; Diet, High-Fat; Humans; Inflammation, metabolism; Insulin, secretion; Interleukin-1beta, metabolism; Islets of Langerhans, metabolism; Mice; Mitochondria, metabolism; Renin-Angiotensin System, physiology; Vasoconstriction, drug effects
Pathological activation of the renin-angiotensin system (RAS) is associated with the metabolic syndrome, and the new onset of type 2 diabetes can be delayed by RAS inhibition. In animal models of type 2 diabetes, inhibition of the RAS improves insulin secretion. However, the direct effects of angiotensin II on islet function and underlying mechanisms independent of changes in blood pressure remain unclear. Here we show that exposure of human and mouse islets to angiotensin II induces interleukin (IL)-1-dependent expression of IL-6 and MCP-1, enhances beta-cell apoptosis, and impairs mitochondrial function and insulin secretion. In vivo, mice fed a high-fat diet and treated with angiotensin II and the vasodilator hydralazine to prevent hypertension showed defective glucose-stimulated insulin secretion and deteriorated glucose tolerance. Application of an anti-IL-1beta antibody reduced the deleterious effects of angiotensin II on islet inflammation, restored insulin secretion, and improved glycemia. We conclude that angiotensin II leads to islet dysfunction via induction of inflammation and independent of vasoconstriction. Our findings reveal a novel role for the RAS and an additional rationale for the treatment of type 2 diabetic patients with an IL-1beta antagonist.
Publisher American Diabetes Association
ISSN/ISBN 0012-1797 ; 1939-327X
edoc-URL https://edoc.unibas.ch/61696/
Full Text on edoc No;
Digital Object Identifier DOI 10.2337/db14-1282
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/25352639
Document type (ISI) Journal Article