ROS-dependent PRR Expression in Immune Cells in a Diabetes Mellitus Rat Model

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Introduction: Diabetes Mellitus (DM) is a major public health problem. Either diabetes mellitus type 1, type 2, gestational or other, is a complex syndrome characterized by hyperglycemia, polydipsia, polyphagia, polyuria, and loss weight. DM can lead to complications in which oxidative stress has been related. There is a bulk of evidence suggesting that glucose can stimulate by itself or by several enzymatic cascades the overproduction of reactive oxygen species (ROS), as well as the imbalance in the antioxidant defense mechanisms. Numerous studies have proposed the administration of antioxidants such as vitamins C and E to prevent or avoid progression of complications derived from DM. It has been reported that activation of the renin-angiotensin system (RAS) plays a significant role in the pathophysiology of DM. A new component appears important: the Prorrenin / Renin Receptor (PRR), initially found in the kidney, but more recently detected in cells of the immune system. There is evidence showing the PRR as an inflammatory component in DM models because besides being constitutively expressed in T cells, NK and macrophages, it regulates cytokine levels. However it is unknown, if oxidative state in diabetes is responsible for the PRR-expression elevation. **Objective:** To evaluate, in a rat DM model, ROS effect on the expression of PRR in cells of the immune system.

Material and Methods: Wistar male rats, 250-300 g weight, were used in four groups: DM rats with antioxidants (H + A), DM rats without antioxidants (H + 0), normoglycemic rats with antioxidants (Sh + A) and normoglycemic rats without antioxidants (Sh + 0). This investigation was conducted in conformance with ethical and animal care principles under mexican norm (NOM-062-ZOO-1999). Hyperglycemia was induced by streptozotocin (STZ) IV injection, at a dose of 65mg / kg using citrate buffer, pH 4.2 as vehicle. After measurement of glucose level, 500mg / kg of vitamin C and 700mg / kg of vitamin E were administered daily for 8 or 15 days, p.o. At the end of the 8 or 15 days treatment, spleen and blood were obtained. SOD, CAT and GPX activity was determined in the spleen, as well as the total antioxidant activity by ELISA and lipid peroxidation by MDA-TBARS; total ROS were quantified by flow cytometry. In blood,

the expression of TNF-α, IL-6, IL-10 and TGF-β was measured by qRT-PCR. The expression of PRR in T cells, NK and macrophages was performed by cytometry.

Results: Hyperglycemia presented an average value of 400 mg/dL in diabetic rats. There was a significant decrease of the enzymatic activity in the H+0 group compared to the control (Sh+0), while in the H+A group augmented. Lipid peroxidation was risen in the H+0 groups, but disappeared with vitamins administration at both times. ROS level were significantly high in H groups, but did not increase in H+A group. Pro inflammatory cytokines were elevated in DM rats. In all cell populations, ROS had different effects on PRR expression.

Conclusions: These results suggest that ROS play a significant role in DM controlling PRR expression and possibly in the onset of complications derived from this disease.

Keywords: Reactive oxigen species, rat model, diabetes mellitus, dependent ,Prorrenin / Renin Receptor, immune response