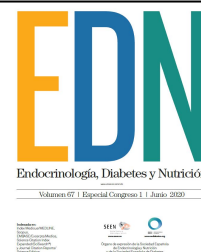




Endocrinología, Diabetes y Nutrición



O-15 - FN14 DRIVES THE DOWNREGULATION OF THE ANTIAGING FACTOR KLOTHO IN DIABETIC NEPHROPATHY

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Resumen

Introduction and objectives: Hyperglycemia is the key driver of diabetic complications. Diabetic nephropathy (DN) is one of the main complications of diabetes, the most common cause of end-stage renal disease and a growing cause of death worldwide. A better understanding of secondary mediators of injury may lead to new therapeutic strategies. TWEAK is a cytokine of the TNF superfamily that activates the Fn14 receptor and contributes to kidney injury and experimental proteinuric nephropathies. However, the role of the TWEAK/Fn14 system in the DN is unknown.

Methods: To assess the functional implications of Fn14 in DN, type 1 diabetes was induced in wild type and Fn14 knockout mice by Streptozotocin administration. Mice were studied after 9 weeks of diabetes. Immunohistochemistry, Western blotting and RT-PCR were performed in kidney tissue. The effect of high glucose and glucose degradation products was also studied in murine proximal tubular epithelial cells and in human glomerular podocytes.

Results: Experimental diabetes resulted in increased kidney expression of the TWEAK receptor Fn14 mRNA and protein. Immunohistochemistry confirmed the increased expression of Fn14 protein and localized it to tubular cells. Additionally, diabetes caused a kidney inflammatory response characterized by upregulation of the chemokine expression (MCP-1, RANTES) and decreased the expression of the anti-aging factor Klotho. Genetic Fn14 deficiency resulted in a less severe DN as assessed by lower RANTES and MCP-1 expression as well as by preservation of Klotho expression. In culture, high glucose also induced Fn14 expression in proximal tubular cells and human podocytes. In addition, 3,4-dideoxyglucosone-3-ene (3,4-DGE), the most toxic product of glucose degradation, also induced the expression of Fn14. Furthermore, TWEAK downregulated Klotho expression in tubular cells.

Conclusions: These data suggest that Fn14 may play a role in the pathogenesis of DN by promoting kidney inflammation and decreasing the antiaging factor Klotho. The decrease in Klotho may be one of the factors contributing to the accelerated aging of DN patients.