A Nonerythropoietic Peptide Analog of Erythropoietin Decreases Susceptibility to Diet-Induced Insulin Resistance

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Erythropoietin (EPO) has multiple biological functions, including the modulation of glucose metabolism (Choi D. et al., 2011). However, so far the clinical transferability of EPO effects on insulin sensitivity is limited, mainly because of the well-known effects of EPO on hematopoiesis. The erythropoietic effects of EPO would be mediated by the classic EPO receptor homodimer, whereas the tissue-protective effects are mediated by a hetero-complex between the EPO receptor monomer and the β-common receptor (termed "tissue-protective receptor") (Patel NS. et al., 2011). Here, we have investigated the effects of a novel, selective-ligand of the tissue-protective receptor (pyroglutamate helix B surface peptide [pHBSP]) in a mouse model of insulin resistance evoked by chronic exposure to an unhealthy Western diet, featuring both high cholesterol and sucrose (HCS) intake. Male C57Bl/6J mice were maintained on a HCS diet for 22 weeks and pHBSP (30 μg/kg/day s.c.) was administered for the last 14 weeks of the dietary manipulation. At the end of the treatment, serum and urine were collected for biochemical analysis. Mice fed the HCS diet exhibited hyperinsulinemia, impaired glucose tolerance, hyperlipidemia and hypoadiponectinemia. These effects were associated with a renal dysfunction, as suggested by increase in serum urea and creatinine levels and significant reduction in creatinine clearance. pHBSP improved lipid metabolism, insulin responsiveness and renal function. Interestingly, the experimental diet caused a marked increase in serum concentrations of the newly identified member of the fibroblast growth factor (FGF) superfamily, FGF-21, a myokine involved in the control of impaired glucose homeostasis, and the well-known cytokine interleukin-6 (IL-6). pHBSP administration significantly decreased the serum levels of the two cytokines. In conclusion, this is the first study showing that the nonerythropoietic erythropoietin derivative pHBSP protects against the metabolic abnormalities caused by chronic HFCS exposure by affecting multiple levels of the insulin signaling and inflammatory cascades.

Choi D. et al., (2011) *Curr Diabetes Rev.* 7, 284-90.
Patel NS. et al., (2011) *Ann Intensive Care*. 1, 40.