Relaxin Improves Multiple Markers of Wound Healing and Ameliorates the Disturbed Healing Pattern of Genetically Diabetic Mice

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Diabetic mice are characterized by a disrupted expression pattern of vascular-endothelial-growth-factor (VEGF), and impaired vasculogenesis during healing (Altavilla et al., 2001). Experimental evidence suggest that relaxin (RLX) can improve several parameters associated with wound healing (Goodson et al., 1977). Therefore, we investigated the effects of porcine derived relaxin in diabetes-related wound healing defects in genetically diabetic mice (Bohlen et al., 1979). An incisional wound model was produced on the back of female diabetic C57BL/KsJ-m+/+*Lept*^{db} (db^{+}/db^{+}) mice and their normal littermates ($db^{+/+}m$). Animals were treated daily with porcine RLX (25μg mouse/day/s.c.) or its vehicle. Mice were killed on 3, 6 and 12 days after skin injury for measurements of VEGF mRNA and protein synthesis, stromal cell-derived factor-1α (SDF-1α) mRNA and endothelial nitric oxide synthase (eNOS) expression. Furthermore, we evaluated wound-breaking strength, histological changes, angiogenesis and vasculogenesis at day 12. Diabetic animals showed a reduced expression of VEGF, eNOS and SDF-1α compared to non diabetic animals. At day 6, RLX administration resulted in an increase in VEGF mRNA expression and protein wound content, in eNOS expression and in SDF-1α mRNA. Furthermore the histological evaluation indicated that RLX improved the impaired wound healing, enhanced the staining of matrix metalloproteinase-11 (MMP-11) and increased wound breaking strength at day 12 in diabetic mice. Immunohistochemistry showed that RLX in diabetic animals augmented new vessels formation by stimulating both angiogenesis and vasculogenesis. RLX significantly reduced the time to complete skin normalization and this effect was abrogated by a concomitant treatment with antibodies against VEGF and CXCR4, the SDF-1α receptor. These data strongly suggest that RLX may have a potential application in diabetes-related wound disorders.

References

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