Activation of the EPOR-b common receptor complex by cibinetide ameliorates impaired wound healing in genetically diabetic mice.

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Erythropoietin (EPO) triggers the dimerized EPO receptor (EPOR2) to induce erythropoiesis, but its extra-hematopoietic and tissue protective effect is mediated by the EPOR-□□common receptor complex (EPO-□cR). The wound healing stimulating effect of cibinetide were studied in diabetic (db+/db+) animals. An incisional wound healing model was induced on the back of female db+/db+ mice and their normal littermates (WT). Animals were treated daily with cibinetide (30 □g/ml/s.c.) or vehicle and were euthanized at 3, 7 and 14 days after the wound healing procedures to measure Vascular Endothelial Growth Factor (VEGF), malondialdehyde (MAL), Phospho-Akt (pAkt), phospho e-NOS (p-eNOS), nitrates levels, histological changes, angiogenesis by CD31 immunochemistry, and wound breaking strength. The time to complete skin closure was also monitored. Throughout the wound healing process and in comparison with normoglycaemic animals, diabetic animals treated with vehicle showed reduced VEGF and increased MAL levels. They showed also reduced expression of pAkt and peNOS, decreased levels of nitrates poor re-epitheliziation of the wounds, blunted CD31 expression and impaired wound breaking strength. Cibenitide treatment increased VEGF, reduced MAL levels, augmented p-Akt and p-eNOS expression, enhanced nitrate skin content, improved the disturbed healing patterns, stimulated angiogenesis, and normalized wound breaking strength. Finally, in a comparison experiment with recombinant human EPO (400 IU/kg/day/sc) cibinetide was superior in improving the time to complete wound healing.

The results suggest that the IRR is involved in wound healing and that cibinetide may represent an interesting strategy to treat diabetes induced wound healing disorders.