電気穿孔法を用いたヒト胎盤成長因子２の遺伝子導入による糖尿病性神経障害の改善

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Placental growth factor-2 gene transfer by electroporation restores diabetic sensory neuropathy in mice

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ABSTRACT: Placental growth factor-2 (PlGF-2) exhibits neurotrophic activity in dorsal root ganglion (DRG) neurons through the neuropilin-1 (NP-1) receptor *in vitro*. To examine the potential utility of PlGF-2 therapy for treating diabetic neuropathy, we performed intramuscular PlGF-2 gene transfer by electroporation, and examined its effects on sensory neuropathy in diabetic mice. PlGF-2 was overexpressed in the tibial anterior (TA) muscles of streptozotocin-induced diabetic mice with hypoalgesia using a PlGF-2 plasmid injection with electroporation. The nociceptive threshold was measured using a paw-pressure test. In addition, we overexpressed PlGF-1, an isoform of PlGF that does not bind NP-1. The sciatic nerve and skin were examined 3 weeks after PlGF-2 electro-gene transfer. The overexpression and secretion of PlGF-2 in TA muscles were confirmed by an increase in PlGF levels in TA muscles and plasma, and strongly PlGF positive myofibers in TA muscles. Two weeks after electro-gene transfer into the bilateral TA muscles, the previously elevated nociceptive threshold was found to be significantly decreased in all treated mice. PlGF-1 gene transfer by electroporation did not significantly decrease the nociceptive threshold in diabetic mice. No increase in the number of endoneurial vessels in the sciatic nerve was found in the PlGF-2 plasmid-electroporated mice. A reduction of area of immunoreactivity in epidermal nerves in diabetic mice was restored by PlGF-2 gene transfer. These findings suggest that PlGF-2 electro-gene therapy can significantly ameliorate sensory deficits (*i.e.* hypoalgesia) in diabetic mice through NP-1 in DRG and peripheral nerves.

抄録　ストレプトゾトシン誘発糖尿病マウスの前脛骨筋内に PlGF-1 あるいは 2 遺伝子を導入し、糖尿病性神経障害に対する改善効果を検討した。NP-1 受容体に結合しない PlGF-1 の遺伝子導入では痛覚鈍麻に変化は認められなかったが、同受容体に結合する PlGF-2 の遺伝子導入においては導入 2 週後より痛覚鈍麻は改善した。また、PlGF-2 の

遺伝子導入においては、足底表皮の自由神経終末の減少は回復した。このとき、坐骨神経内の血管数には変化は認められなかった。これらの結果から、PlGF-2 の遺伝子導入による糖尿病性神経障害の進展抑制は、後根神経節および末梢神経の NP-1 受容体を介して作用していることが考えられた。

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