Pioglitazone improves erectile function after cavernosal nerve injury through an insulin-like growth factor-1 (IGF-1) pathway

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**Introduction**

_Efficacy of pioglitazone on erectile function recovery in a rat model of cavernous nerve injury._

Aliperti LA¹, Lasker GF¹, Hagan SS¹, Hellstrom JA¹, Gokce A², Trost LW³, Kadowitz PJ⁴, Sikka SC¹, Hellstrom WJ⁵.

**Author information**

**Abstract**

**OBJECTIVE:** To examine the effect of pioglitazone on erectile function in a rat model of postprostatectomy erectile dysfunction.

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_Pioglitazone Enhances Survival and Regeneration of Pelvic Ganglion Neurons After Cavernosal Nerve Injury._

Katz EG¹, Moustafa AA², Heidenberg D¹, Haney N¹, Peak T¹, Lasker GF¹, Knoedler M¹, Rittenberg D¹, Rezk BM³, Abd Elmageed ZY¹, Yafi FA¹, Sikka S¹, Abdel-Mageed AB¹, Hellstrom WJ⁴.

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**Abstract**

**OBJECTIVE:** To investigate the effects of pioglitazone on pelvic ganglion neurons in a rat model of bilateral cavernosal nerve crush injury (BCNI), thereby elucidating the actions of pioglitazone in preventing post-prostatectomy neurogenic erectile dysfunction.
Introduction

• Pioglitazone (Actos, Takeda Pharmaceuticals)
  – Diabetic treatment (TZD)
    • Decreases peripheral insulin resistance
  – Peroxisome proliferator-activated receptor gamma (PPARγ)
  – Vasculoprotective and neuroprotective in cerebrovascular accident models

Introduction

- Pioglitazone upregulated IGF1 in the human aortic arch [1]
- IGF1 stimulated nerve growth in:
  - Sciatic nerve [2]
  - Optic nerve [3]

Purpose

**Aim:** determine the neuro-regenerative mechanism of Pioglitzazole after nerve crush injury in the rat model

**Hypothesis:** Pioglitzazole improves cavernosal nerve outcome through an IGF-1 mediated pathway
Methods

• Animals Groups
  1. Sham (n=5)
  2. Bilateral cavernosal nerve crush (BCNI) (n=7)
  3. BCNI + Pioglitazone (n=7)
  4. BCNI + Pioglitazone + JB-1 (IGF-1 antagonist) (n=7)

• 14D oral treatment PBS or Pioglitazone
  – 6.5mg/kg

• 14D subcutaneous treatment: saline or JB-1 (IGF-1 antagonist)
  – 100mg/kg
Methods

ICP/MAP at 2 weeks

- Sham
- BCNI
- BCNI+PIO
- BCNI+PIO+JB1

The chart shows the ICP/MAP at 2 weeks for different conditions and voltage levels (7.5 V, 5 V, 2.5 V). The bars represent the mean values with error bars indicating the standard deviation. Asterisks (*) denote statistically significant differences among the groups.
Area Under the Curve at 2 weeks

- Sham
- BCNI
- BCNI+PIO
- BCNI+PIO+JB1

* Significant differences
## Results: Western Blot

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- **nNOS (150KD)**
- **IGF-I A (22KD)**
- **IGF-I B (17KD)**
- **P44/42-Erk1/2**
- **GAPDH (37KD)**
Tanja Vogel (2013). Insulin/IGF-Signaling in Embryonic and Adult Neural Proliferation and Differentiation in the Mammalian Central Nervous System, Trends in Cell Signaling Pathways in Neuronal Fate Decision, Dr Sabine Wislet-Gendebien (Ed.), InTech, DOI: 10.5772/54946.
Results
Conclusions

• Pioglitazone treatment after BCNI in the rat model restores erectile function equivalent to sham levels

• **JB-1 (competitive antagonist) reversed Pioglitazone’s beneficial effect after BCNI in the rat model**

• Therefore, Pioglitazone’s positive effect on the cavernous nerve works through IGF-1

• Pioglitazone promotes neuronal survival and upregulates expression of IGF-1

• Future work will be done to look at IGF-1R

• This data suggests a novel pathway to treat post-RP ED without the toxicity of PGZ
Future Plans

• Local delivery of IGF-1 after cavernosal nerve injury in the rat via PLGA microspheres

• IGF-1 loaded microspheres will be injected directly into the corpora at the time of surgery

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Mughal et al. Effects of Thiazolidinediones on metabolism and cancer: Relative influence of PPARγ and IGF-1 signaling