Comparative Neuroprotective Effects of Methylprednisolone and Rosiglitazone, a Peroxisome Proliferator-activated Receptor-γ Following Spinal Cord Injury

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Introduction: Spinal cord injury (SCI) results in the loss of function below the lesion. Secondary injury following the primary impact includes a number of biochemical and cellular alterations leading to tissue necrosis and cell death. Peroxisome proliferator-activated receptor (PPAR) is a ligand-activated transcription factor of nuclear hormone receptor superfamily and plays a significant role in glucose and lipid homeostasis. PPARγ agonists have been reported to be applied in several models of central nervous system injury and disease. Presently, to explore the possibility of PPARγ agonists applying in SCI, we compared the neuroprotective effects of methylprednisolone (MPSS) and PPARγ agonist rosiglitazone (ROSG) following spinal cord injury.

Materials and methods: Spinal cord injury was induced by the application of vascular clips (force of 24 g) to the dura via a four-level T5-T8 laminectomy in adult male Sprague-Dawley rats. To gain a better insight into the mechanism of action of the anti-inflammatory effects of rosiglitazone, rosiglitazone was administrated following SCI and the following end points of the inflammatory process were evaluated:
(1) Motor function recovery was studied with the Basso-Beattie-Bresnahan (BBB) scoring system;
(2) Spinal cord inflammation and tissue injury were scored histopathologically and apoptosis were determined by TUNEL staining;
(3) Neutrophil infiltration was assayed by measuring myeloperoxidase (MPO) activity;
(4) The expressoins of the inflammatory markers TNF-α, IL-1β were investigated by immunohistochemistry.
(5) Tissue bax, bcl-2 and HSP70 expression were semi-quantitated by western blotting. The SCI induced rats were delivered with MPSS as control.

Results: Locomotor function progressively improved from day 3 to day 28 in rats suffering from SCI, while a significant improvement was shown in ROSG- or MPSS-treated groups (P<0.05).
Histopathologically, treatment with ROSG or MPSS resulted in a significantly smaller damage, less apoptosis and neutrophil infiltration, compared to vehicle control after SCI insults (P<0.05, respectively). TNF-α and IL-1β were expressed higher in vehicle control rats than in ones with ROSG or MPSS administration (P<0.05). Correspondingly, The ratio of Bax/Bcl-2 and the expression of HSP 70 were higher significantly in vehicle control group than ones in drug delivered groups (P<0.05, respectively). All results showed ROSG significantly decreased spine cord damage, apoptosis and cytokine expression. There showed no significantly difference between MPSS- and ROSG-treated groups (P>0.05).

Conclusion: Taken together, our results clearly demonstrate that administration of ROSG induces significant neuroprotection after SCI insults. Since PPARγ agonists currently are approved for type-2 diabetes treatment by the United States Food and Drug Administration (FDA), they may be considered as a novel target of therapeutic applications in the treatment of spinal cord injury. However, based on the complexity and redundancy of the inflammatory response associated with SCI, it is unlikely that a single target could achieve complete inhibition of inflammation. Thus, it should be point out combined treatment modalities could promise better therapeutic effects.