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BRAIN RESEARCH

Research Report

Rosiglitazone, a PPAR gamma agonist, attenuates inflammation after surgical brain injury in rodents

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ABSTRACT

Introduction: Surgical brain injury (SBI) is unavoidable during many neurosurgical procedures. This inevitable brain injury can result in post-operative complications including brain edema, blood–brain barrier disruption (BBB) and cell death in susceptible areas. Rosiglitazone (RSG), a PPAR-γ agonist, has been shown to reduce inflammation and provide neuroprotection in experimental models of ischemia and intracerebral hemorrhage. This study was designed to evaluate the neuroprotective effects of RSG in a rodent model of SBI. Methods: 65 adult male Sprague–Dawley rats were randomly divided into sham, vehicle and treatment groups. RSG was administered intraperitoneally in two dosages (1 mg/kg/dose, 6 mg/kg/dose) 30 min before surgery, and 30 min and 4 h after surgery. Animals were euthanized 24 h following neurological evaluation to assess brain edema and BBB permeability by IgG staining. Inflammation was examined using myeloperoxidase (MPO) assay and double-labeling fluorescent immunohistochemical analysis of IL-1β and TNF-α. Results: Localized brain edema was observed in tissue surrounding the surgical injury. This brain edema was significantly higher in rats subjected to SBI than sham animals. Increased IgG staining was present in affected brain tissue; however, RSG reduced neither IgG staining nor brain edema. RSG also did not improve neurological status observed after SBI. RSG, however, significantly attenuated MPO activity and qualitatively decreased IL-1β and TNF-α expression compared to vehicle-treated group. Conclusion: SBI causes increased brain edema, BBB disruption and inflammation localized along the periphery of the site of surgical resection. RSG attenuated inflammatory changes, however, did not improve brain edema, BBB disruption and neurological outcomes after SBI.

1. Introduction

Neurosurgical operations can result in inevitable brain injury due to surgical trauma, retractor stretch, intraoperative hemorrhage and electrocautery damage (Andrews and Muto, 1992; Solaroglu et al., 2004, Jadhav et al., 2007a). This surgical brain injury (SBI) is unavoidable (Deletis and Sala, 2001) and results in brain edema, disruption of blood–brain barrier (BBB), oxidative stress, and cell death in the vulnerable functional tissue along the periphery of surgical resection (Matchett et al.,

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2006; Jadhav et al., 2007a; Lo et al., 2007). SBI not only has medical significance but also has medicolegal implications due to the practice of 'defensive medicine' which results in excess expenditure to the tune of $ 70–126 billion a year ("Addressing the New Health Care Crisis," U.S. Department of Health and Human Services, March 2003).

Rosiglitazone (RSG), a peroxisome proliferating activating receptor-γ (PPAR-γ) agonist, is shown to be neuroprotective in focal cerebral ischemia and intracerebral hemorrhage (Allahtavakoli et al., 2006; Chen et al., 2006; Luo et al., 2006; Pereira et al., 2006; Zhao et al., 2007). RSG is a constituent of the thiazolidinediones nuclear hormone receptor superfamily and is known for its anti-inflammatory actions via activation of PPAR-γ. The activation of PPAR-γ leads to the inhibition of the inflammatory NFkB pathway (Luo et al., 2006; Tureyen et al., 2007). Thus, RSG attenuates the expression of pro-inflammatory genes and cytokine production by regulating ligand activation of transcription factors (Luo et al., 2006; Chen et al., 2006).

Inflammation is a key component of brain injuries resulting from different etiologies such as trauma, ischemia, neurodegeneration, and excitotoxicity (Esiri, 2007; Wang et al., 2007; Williams et al., 2007). Acute inflammation involves the activation of a range of cells including neutrophils and microglia, in addition to inflammatory mediators such as cytokines and chemokines (Wang et al., 2007), which can contribute to disruption of BBB leading to brain edema as well as neuronal damage (Stamatovic et al., 2006). Thus, inflammatory processes can exacerbate brain injury and worsen the neurological outcomes (Luo et al., 2006). In the present study we hypothesized that SBI causes inflammation in susceptible brain tissue and RSG provides neuroprotection via its anti-inflammatory actions.

2. Results

2.1. *Brain water content was not attenuated with Rosiglitazone treatment*

Brain water content in the frontal ipsilateral lobe (susceptible to SBI) was significantly higher in all animals subjected to SBI as compared with sham surgery group. However, there was no significant difference in brain water content between vehicle-treated group and groups treated with either doses of RSG (1 mg/kg, 6 mg/kg) (Fig. 1). Other areas of the brain were also evaluated, however, there were no significant differences observed in brain water content between sham surgery, vehicle-treated and RSG treated groups (contralateral frontal lobe data in Fig. 1, other brain regions not shown) similar to previous reports (Jadhav et al., 2007a).

2.2. *Rosiglitazone did not reduce blood–brain barrier permeability*

The breakdown of the BBB was qualitatively determined by IgG staining similar to previous reports (Jadhav et al., 2007b; Yamaguchi et al., 2007). The frontal contralateral lobe which served as control did not show any IgG staining (brown staining). In contrast, in the frontal ipsilateral lobe, IgG serum proteins were increasingly present surrounding the site of resection (Fig. 2). Higher magnification indicated that that the extravasation of IgG was more around the micro vasculature (Fig. 2). However, RSG treatment (6 mg/kg) did not show any qualitative difference in IgG staining thus, indicating that it did not decrease BBB permeability after SBI.

2.3. *Inflammation was reduced with Rosiglitazone treatment*

Myeloperoxidase (MPO), a marker for the infiltration of neutrophils, was assayed for quantitative indication of the presence of inflammation in the ipsilateral frontal lobes from different groups. MPO observed at high optical density (460 nm) signifies an increased presence of inflammation. Vehicle-treated groups had a significantly higher MPO (6.85 ± 1.35 U/g) compared to sham surgery groups (0.22 ± 0.03 U/g). In RSG (1 mg/kg) treated groups, there was a significant decrease in MPO (2.15 ± 0.82 U/g) compared with vehicle-treated groups demonstrating its anti-inflammatory properties (Fig. 3A).

Immunohistochemical analysis of well known inflammatory markers TNF-α and IL-1β indicated that these markers were increased in the neurons (NeuN, neuronal marker) in the affected brain tissue in the vehicle-treated rats. However, in animals treated with RSG (6 mg/kg), there appeared to be decreased levels of both inflammatory markers in the affected

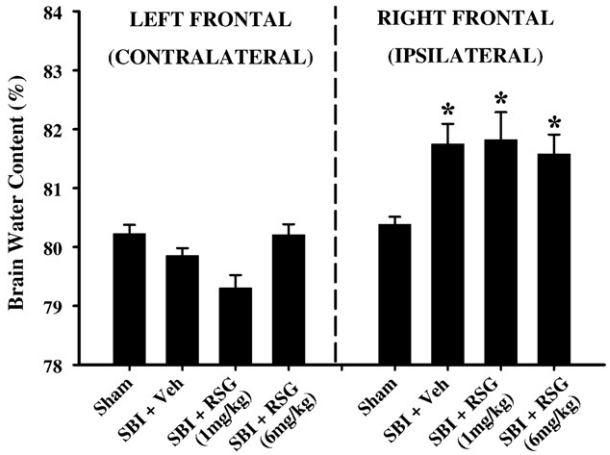

Fig. 1 – Effect of RSG on brain water content. The figure shows quantified data representing brain water content (brain edema) in the contralateral and ipsilateral frontal lobes of the brain at 24 h after SBI. There is no significant difference in the brain water content between the sham surgery, vehicle-treated and RSG treated groups (1 mg/kg and 6 mg/kg) in the contralateral frontal lobe. The ipsilateral frontal lobes show significantly higher brain water content in the vehicle and RSG treated groups (1 mg/kg and 6 mg/kg) as compared to the sham surgery group. However, there is no significant difference between the RSG treated groups and vehicle-treated groups. $p < 0.05$, (*) denotes significant difference compared to sham surgery group. 'n' number is as follows: sham surgery = 8, SBI + vehicle = 7, SBI + RSG 1 mg/kg = 4, SBI + RSG 6 mg/kg = 8.