The Journal of Pain, Vol 9, No 7 (July), 2008: pp 639-649
Available online at www.sciencedirect.com

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Intrathecal Rosiglitazone Acts at Peroxisome Proliferator–Activated Receptor-γ to Rapidly Inhibit Neuropathic Pain in Rats

Sajay B. Churi, Omar S. Abdel-Aleem, Kiranjeet K. Tumber, Heather Scuderi-Porter, and Bradley K. Taylor

Department of Pharmacology, School of Medicine, Tulane University, New Orleans, Louisiana.

Abstract: **In this report, we demonstrate the transcription, expression, and DNA-binding properties of the peroxisome proliferator–activated receptor (PPAR)-γ subtype of the peroxisome proliferator–activated nuclear receptor family to the spinal cord with real-time PCR, Western blot, and electrophoretic mobility shift assay. To test the hypothesis that activation of spinal PPAR-γ decreases nerve injury–induced allodynia, we intrathecally administered PPAR-γ agonists and/or antagonists in rats after transection of the tibial and common peroneal branches of the sciatic nerve. Single injection of either a natural (15-deoxy-prostaglandin J2, 15d-PGJ2) or synthetic (rosiglitazone) PPAR-γ agonist dose-dependently decreased mechanical and cold hypersensitivity. These effects were maximal at a dose of 100 μg and peaked at ~60 minutes after injection, a rapid time course suggestive of transcription-independent mechanisms of action. Concurrent administration of a PPAR-γ antagonist (bisphenol A diglycidyl ether, BADGE) reversed the effects of 15d-PGJ2 and rosiglitazone, further indicating a receptor-mediated effect. In animals without nerve injury, rosiglitazone did not alter motor coordination, von Frey threshold, or withdrawal response to a cool stimulus. Intraperitoneal and intracerebroventricular administration of PPAR-γ agonists (100 μg) did not decrease mechanical and cold hypersensitivity, arguing against effects subsequent to diffusion from the intrathecal space. We conclude that ligand-induced activation of spinal PPAR-γ rapidly reverses nerve injury–induced mechanical allodynia. New or currently available drugs targeted at spinal PPAR-γ may yield important therapeutic effects for the management of neuropathic pain.**

Perspective: ***PPAR-γ receptor agonists such as rosiglitazone and pioglitazone are approved as insulin sensitizers by the United States Food and Drug Administration. We demonstrate PPAR-γ expression in the spinal cord and report that activation of these receptors inhibits allodynia. BBB-permeant PPAR-γ agonists may yield important therapeutic effects for the management of neuropathic pain.***

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Key words: *Allodynia, hyperalgesia, rat, 16-deoxy-prostaglandin-J2, spared nerve injury, pioglitazone.*

Peroxisome proliferator–activated receptors (PPARs) are transcription factors belonging to the nuclear receptor superfamily.[15] PPARs are activated by fatty acids, eicosanoids, and synthetic ligands. Activated PPARs form functional heterodimers with retinoid X receptors (RXR). This complex interacts with various coactivators and a specific peroxisome proliferator response element (PPRE) on the promoter region of target genes to alter transcription.[34]

Three PPARs have been identified: α, β/δ, and γ.[2,22] The PPAR-γ isotype mediates numerous physiological functions; of particular clinical significance is its role as a lipid sensor. PPAR-γ activation leads to adipocyte differentiation and drives the gene expression of enzymes that facilitate lipid uptake and synthesis.[16] Dysregulation of PPAR-γ function is associated with numerous diseases such as type 2 diabetes. Indeed, synthetic PPAR-γ agonists of the thiazolidinedione (TZD) class act as insulin

Received October 14, 2007; Revised February 1, 2008; Accepted February 2, 2008.

Supported by National Institutes of Health grants DA10356, NS43383, and DA19656 (B.K.T.).

Drs. Churi and Abdel-Aleem contributed equally to this work.

Address reprint requests to Dr. Bradley K. Taylor, Department Pharmacology, SL83, Tulane University Health Sciences Center, New Orleans, LA 70112. E-mail: taylorb@tulane.edu

1526-5900/$34.00

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doi:10.1016/j.jpain.2008.02.002

sensitizers. Although our understanding of the glucose-lowering properties of PPAR-γ ligands remains an intense area of investigation,[31] TZDs such as rosiglitazone and pioglitazone represent an important pharmacotherapy for the treatment of glucose intolerance.[21]

It is becoming increasingly clear that PPAR-γ ligands represent a promising therapeutic strategy for other diseases as well, including atherosclerosis, cancer, cardiovascular complications, inflammation, spinal cord injury, and neurodegenerative disorders such as Alzheimer's disease.[1] Our previous data suggested that PPAR-α ligands exert additional central nervous system (CNS) actions on nociceptive signaling pathways,[37] possibly by acting at PPARs in the brain.[36] In specific, we reported that PPAR-α ligands reduced behavioral signs of inflammatory pain in rats,[37] findings that were recently confirmed with PPAR-α deletion-mutant mice.[18] Whether PPAR-γ ligands can similarly exert analgesic actions is unclear. An important clue comes from very recent studies in a rat model of spinal cord injury (SCI). Park et al[26] found that pretreatment with the TZD pioglitazone prevented numerous consequences of SCI, including neuronal damage, motor dysfunction, myelin loss, inflammation, and most notably, thermal hyperalgesia. Coadministration of the PPAR-γ antagonist GW9662 reversed these actions. Whether pioglitazone acted directly at spinal cord sites to reduce nociceptive signalling cannot be deduced from these studies, however, because of its multiple effects on SCI pathology. To directly address this question, the present studies were designed to test the hypothesis that spinally directed delivery of PPAR-γ ligands decreases allodynia and hyperalgesia in an animal model of peripheral neuropathic pain. Furthermore, we extend a single immunohistochemical finding suggesting that PPAR-γ immunoreactivity in a key site of pain transmission, lamina II of the dorsal horn,[25] with additional real-time PCR, Western, and EMSA studies.

Materials and Methods

Animals

Male Sprague-Dawley rats (Charles River Laboratories, Inc., Wilmington, MA) weighed 280 to 320 g at the time of nerve injury and intrathecal catheter implantation and 340 to 380 g during pharmacological testing. Animals were housed in individual cages on a 12-hour light/dark cycle starting at 6 AM and were given food and water ad libitum. All animal use protocols were approved by the Institutional Animal Care and Use Committee (IACUC) of Tulane University.

Spared Nerve Injury Surgery

Rats were anesthetized with isoflurane (5% induction, then 1.5% maintenance in oxygen). As previously described,[7] an incision was made in the skin at the level of the trifurcation of the left sciatic nerve. The overlying muscles were retracted, exposing the common peroneal, tibial, and sural nerve. The common peroneal and tibial nerves were ligated with 6-0 silk (Ethicon, Somerville, NJ); the knot and adjacent nerve (2 mm) were then transected. Care was taken to avoid touching the sural nerve branch. The muscle was next sutured with 4-0 absorbable sutures (Ethicon), and the wound was closed with metal clips.

Intrathecal Catheter Implantation

At the time of nerve injury, animals were reanesthetized with isoflurane (Baxter, Deerfield, IL) and then placed in a stereotaxic apparatus (Stoelting, Wood Dale, IL). As previously described,[19] rats were implanted with polyethylene-10 (Clay Adams, Sparks, MD) intrathecal catheters. Briefly, the animal's head was flexed forward in the stereotaxic apparatus. An incision was made in the skin at the back of the rat's head and neck. Next, the cisternal membrane was exposed by dissection. The membrane was gently punctured with the tip of a 15 blade. A 7.5-cm polyethylene-10 catheter (0.28 mm i.d., 0.61 mm o.d.) was passed through the opening in the cisternal membrane and passed into the intrathecal space. The catheter was loosely sutured to subcutaneous tissue and the skin then approximated by using 4-0 absorbable sutures (Ethicon).

Intracerebroventricular Cannula Implantation

Guide cannulas (Plastics One, Roanoke, VA) for intracerebroventricular injection were placed 1 week before experimentation, as previously described.[35] Surgical anesthesia was achieved with isoflurane (5% for induction; 1.5% to 2% for maintenance). Rats were placed in a stereotaxic apparatus fitted with blunt ear bars (Stoelting, Kiel, WI). After an incision to expose the cranium, the dorsal surface of the skull was leveled by zeroing the dorsoventral coordinate at lambda and bregma. A stainless steel guide cannula (Plastics One) was lowered to the right lateral brain ventricle by using the following stereotaxic coordinates: 0.7 posterior to bregma, 1.5 mm lateral from midline and 3.3 to 4.0 below the skull surface.[27] Initial placement of the cannula was verified by slow downward movement of saline when the tubing was opened and raised. The cannula was fixed to the skull with 2 to 3 small screws and dental cement. After hardening of the cement and suturing of the incision, a 30-gauge stylet (Plastics One) was secured within the guide.

Drug Administration and Materials

After surgery, rats were given 7 days to recover before drug administration and experimentation. Drugs were administered via remote injection to minimize effects of animal handling. PE-10 tubing, filled with saline or drug, was used to connect a Hamilton microsyringe to a 30-gauge microinjector; 15 to 20 μL was delivered to the lumbar region of the spinal cord via the intrathecal catheter. Progress of the injection was visually confirmed by observation of movement of a small air bubble within the PE-10 tubing. Injectors were left in place an additional min to minimize backflow within the catheter. The animal was returned to its testing box.

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