Resolvin D1

A New Path to Unleash the Analgesic Potential of Peroxisome Proliferator–activated Receptor-γ for Postoperative Pain in Patients with Diabetes

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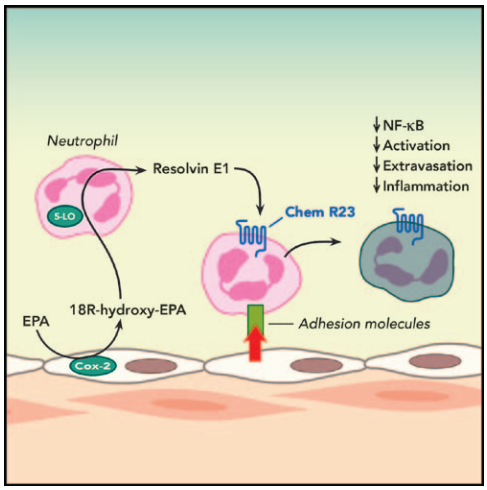
A BASIC science article in this month's issue of ANESTHESIOLOGY provides novel and compelling evidence to adapt clinically approved antidiabetic drugs into an analgesic.[1] Peroxisome proliferator–activated receptors (PPARs) are members of the nuclear receptor superfamily that, unlike plasma membrane receptors that signal through second messengers, function directly as transcription factors that control gene transcription. Activation of the γ isoform (PPARγ) with thiazolidinedione drugs (TZDs) such as rosiglitazone (Avandia®) clearly reduces blood glucose levels in patients with type 2 diabetes. In November 2013, reanalysis of a 6-yr, open-label, randomized, controlled trial on the adverse effects of rosiglitazone failed to confirm the risk of myocardial infarction, leading the U.S. Food and Drug Administration to remove restrictions on the distribution and prescription of rosiglitazone. This move energized research efforts to evaluate the promising alternative therapeutic benefits of TZDs; for example, numerous studies demonstrate that rosiglitazone and another TZD, pioglitazone, reduce behavioral signs of hypersensitivity to mechanical and thermal stimulation in a number of rodent models of inflammatory and neuropathic pain[2–6]; however, few studies have evaluated this class of agents in painful diabetic neuropathy. This gap begins to be filled with this new report from Saito *et al.*[1] in this issue. Their results are clinically relevant because rosiglitazone could readily be added to the anesthesiology cart and used to reduce postoperative pain in patients with type 2 diabetes.



"The authors conclude that resolution of inflammation, disrupted in diabetes, is restored by [these drugs], ... thereby generating analgesia."

The authors have reported that rosiglitazone shifted macrophages from the pronociceptive M1 phenotype to the wound-resolving M2 phenotype and also decreased mechanical hypersensitivity at the site of plantar incision in mice.[4] Saito *et al.* replicated this finding in wild-type mice and then extended it to the db/db genetic mouse model of type II painful diabetic neuropathy. This is important because the wound environment of diabetic patients is characterized by excessive inflammation that may inhibit pain resolution. However, rosiglitazone changed neither the macrophage shift in phenotype nor hyperalgesia in db/db mice. This surprising result compelled the authors to test an innovative and exciting hypothesis that resolvin D1 (RvD1), a key lipid mediator contributing to the resolution of inflammation and pain,[7] is required for rosiglitazone to reduce hyperalgesia. They used RNA interference to reduce the expression of arachidonate 5-lipoxygenase, the biosynthetic enzyme that generates RvD1, and thus prevented the antihyperalgesic actions of rosiglitazone in normoglycemic mice. Thus, diabetes may interrupt synthesis of resolving D1, as suggested by low levels of its biosynthetic precursor (17-hydroxydocohexaenoic acid) in wounds of db/db mice,[8] which appears to prevent facilitation of rosiglitazone analgesia in diabetic mice.

The study by Saito *et al.* is a *tour de force* that extends our understanding of the peripheral mechanisms by which local administration of PPARγ agonists inhibit persistent pain. In a rigorous, well-controlled experimental design with three independent variables (rosiglitazone *vs.* vehicle, RvD1 *vs.* vehicle, and db/db *vs.* nondiabetic genetic controls), the ability of rosiglitazone to reduce mechanical hypersensitivity was restored in diabetic mice upon coadministration with RvD1. Furthermore, immunohistochemical and gene expression analyses of inflammatory processes in the injured tissue demonstrated that RvD1

Image: A. Johnson.

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Accepted for publication July 13, 2015. From the Department of Physiology, University of Kentucky College of Medicine, Lexington, Kentucky.

 Anesthesiology 2015; 123:1231-2

restored the rosiglitazone-mediated shift of macrophage phenotype from M1 to M2, attenuation of neutrophil infiltration, and macrophage clearance of apoptotic neutrophils. The authors conclude that resolution of inflammation, disrupted in diabetes, is restored by exogenous RvD1, thus promoting PPARγ-mediated macrophage shift to the M2 phenotype and thereby generating analgesia.

One shortcoming of the study by Saito *et al.* is the exclusive use of reflex measures of pain hypersensitivity. A recent review of preclinical models of painful diabetic neuropathy suggests the modeling of stimulus-independent and cognitive-affective components of pain in basic science studies so as to more closely reflect the human condition.[9] Another unresolved issue is whether PPARγ really does mediate the actions of rosiglitazone (*e.g.*, by blocking its effects with receptor antagonists) and whether nongenomic mechanisms are recruited upon PPARγ activation. Recent studies find that pioglitazone both rapidly (within minutes)[6] and persistently[5] reduces neuropathic pain through translation-independent and translation-dependent pathways, respectively. Furthermore, because of the use of just a single dose of rosiglitazone and RvD1, Saito *et al.* fall short in determining whether the analgesic actions of rosiglitazone and RvD1 are additive or synergistic. These questions await further study and will be critical to elucidate the molecular mechanisms by which rosiglitazone and RvD1 interact. Regardless, Saito *et al.* complement a growing body of literature extolling PPARγ as an attractive target for inflammation and pain control. Indeed, the antiinflammatory and antihyperalgesic actions of PPARγ agonists extend beyond peripheral tissues to the spinal cord and brain.[2,10] This raises the compelling idea that preemptive oral administration of a TZD, for several days before and then continuing after surgery, could act at both peripheral and central sites to reduce the intensity and/or duration of postoperative pain in patients with type 2 diabetes. With respect to recent reports that long-term administration of pioglitazone acts at PPARγ in the dorsal horn to inhibit spinal pain transmission after peripheral nerve injury,[5] it will be important to determine whether TZDs similarly decrease neuropathic pain and central sensitization associated with type 2 diabetes.

Acknowledgments

Supported by grant R01NS62306 from the National Institutes of Health (Bethesda, Maryland) to Dr. Taylor and with a critical reading of the manuscript by Ryan Griggs, M.S. (Department of Physiology, University of Kentucky, Lexington, Kentucky).

Off-Label Use of Drugs: neither rosiglitazone nor pioglitazone is labeled for the treatment of pain.

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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References

1. Saito T, Hasegawa-Moriyama M, Kurimoto T, Yamada M, Inada E, Kanmura Y: Resolution of inflammation by RvD1 is essential for peroxisome proliferator-activated receptor γ-mediated analgesia during postincisional pain development in type 2 diabetes. Anesthesiology 2015; 123:1420–34
2. Churi SB, Abdel-Aleem OS, Tumber KK, Scuderi-Porter H, Taylor BK: Intrathecal rosiglitazone acts at peroxisome proliferator-activated receptor-γ to rapidly inhibit neuropathic pain in rats. J Pain 2008; 9:639–49
3. Fehrenbacher JC, Loverme J, Clarke W, Hargreaves KM, Piomelli D, Taylor BK: Rapid pain modulation with nuclear receptor ligands. Brain Res Rev 2009; 60:114–24
4. Hasegawa-Moriyama M, Ohnou T, Godai K, Kurimoto T, Nakama M, Kanmura Y: Peroxisome proliferator-activated receptor-γ agonist rosiglitazone attenuates postincisional pain by regulating macrophage polarization. Biochem Biophys Res Commun 2012; 426:76–82
5. Morgenweck J, Griggs RB, Donahue RR, Zadina JE, Taylor BK: PPARγ activation blocks development and reduces established neuropathic pain in rats. Neuropharmacology 2013; 70:236–46
6. Griggs RB, Donahue RR, Morgenweck J, Grace PM, Sutton A, Watkins LR, Taylor BK: Pioglitazone rapidly reduces neuropathic pain through astrocyte and nongenomic PPARγ mechanisms. Pain 2015; 156:469–82
7. Ji RR, Xu ZZ, Strichartz G, Serhan CN: Emerging roles of resolvins in the resolution of inflammation and pain. Trends Neurosci 2011; 34:599–609
8. Tang Y, Zhang MJ, Hellmann J, Kosuri M, Bhatnagar A, Spite M: Proresolution therapy for the treatment of delayed healing of diabetic wounds. Diabetes 2013; 62:618–27
9. Lee-Kubli CA, Mixcoatl-Zecuatl T, Jolivalt CG, Calcutt NA: Animal models of diabetes-induced neuropathic pain. Curr Top Behav Neurosci 2014; 20:147–70
10. Morgenweck J, Abdel-Aleem OS, McNamara KC, Donahue RR, Badr MZ, Taylor BK: Activation of peroxisome proliferator-activated receptor-γ in brain inhibits inflammatory pain, dorsal horn expression of Fos, and local edema. Neuropharmacology 2010; 58:337–45