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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 paper in this month's issue provides novel and compelling evidence to adapt a clinically approved drug to treat diabetes 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 gamma isoform (PPAR γ) with thiazolidinedione drugs (TZDs) such as rosiglitazone (Avandia®) clearly reduce blood glucose levels in patients with type 2 diabetes. In November 2013, re-analysis of a six-year, open label randomized control trial on the adverse effects of rosiglitazone failed to show risk of heart infarct, leading the United States Food and Drug Administration to remove restrictions on the distribution and prescription of rosiglitazone. This move energized research efforts to evaluate 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 pain²⁻⁶; 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* in this issue ¹. Their results are clinically relevant because rosiglitazone could readily be added to the anesthesiology cart and used to reduce post-operative pain in patients with type 2 diabetes.

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 resolving D1 (RvD1), a key lipid mediator contributing to the resolution of inflammation and pain ⁷, is required for rosiglitazone to reduce hyperalgesia. Using an

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Off-Label Use of Drugs: Neither rosiglitazone nor pioglitazone are labeled for the treatment of pain

siRNA approach, they found that reduction in the expression of arachidonate 5-lipoxygenase, the biosynthetic enzyme that generates RvD1, prevented the anti-hyperalgesic actions of rosiglitazone in normoglycemic mice. Thus, diabetes may interrupt synthesis of resolving D1, as suggested by low levels of its biosynthetic precursor (17-HDHA) in wounds of db/db mice ⁸, which appears to prevent facilitation of rosiglitazone analgesia in diabetic mice.

Saito et al is a *tour de force* that extends our understanding of the peripheral mechanisms by which local administration of PPAR γ 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 qPCR analysis of inflammatory processes in the injured tissue demonstrated that RvD1 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 PPAR γ -mediated macrophage shift to the M2 phenotype and thereby generating analgesia.

One shortcoming of *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 PPAR γ really does mediate the actions of rosiglitazone (e.g. by blocking its effects with receptor antagonists) and whether nongenomic mechanisms are recruited upon PPAR γ activation. Recent studies find that pioglitazone both rapidly (within minutes) ⁶ and persistently ⁵ reduces neuropathic pain through translation-independent and dependent pathways, respectively. Furthermore, due to 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 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 PPAR γ as an attractive target for inflammation and pain control. Indeed, the anti-inflammatory and anti-hyperalgesic actions of PPAR γ agonists extend beyond peripheral tissues to the spinal cord or brain ^{2,10}. This raises the compelling idea that pre-emptive 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 post-operative pain in patients with type 2 diabetes. And with respect to recent reports that long-term administration of pioglitazone acts at PPAR γ in the dorsal horn to inhibit spinal pain transmission after peripheral nerve injury ⁵, it will be important to determine whether TZDs similarly decreases neuropathic pain and central sensitization associated with type 2 diabetes.

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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 in press MS#201403068.
2. Churi SB, Abdel-Aleem OS, Tumber KK, Scuderi-Porter H, Taylor BK. Intrathecal rosiglitazone acts at peroxisome proliferator-activated receptor-gamma to rapidly inhibit neuropathic pain in rats. *J Pain*. 2008; 9:639–49. [PubMed: 18387855]
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. [PubMed: 19162071]
4. Hasegawa-Moriyama M, Ohnou T, Godai K, Kurimoto T, Nakama M, Kanmura Y. Peroxisome proliferator-activated receptor-gamma agonist rosiglitazone attenuates postincisional pain by regulating macrophage polarization. *Biochem Biophys Res Commun*. 2012; 426:76–82. [PubMed: 22910418]
5. Morgenweck J, Griggs RB, Donahue RR, Zadina JE, Taylor BK. PPARgamma activation blocks development and reduces established neuropathic pain in rats. *Neuropharmacology*. 2013; 70:236–46. [PubMed: 23415633]
6. Griggs RB, Donahue RR, Morgenweck J, Grace PM, Sutton A, Watkins LR, Taylor BK. Pioglitazone rapidly reduces neuropathic pain through astrocyte and nongenomic PPARgamma mechanisms. *Pain*. 2015; 156:469–82. [PubMed: 25599238]
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. [PubMed: 21963090]
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. [PubMed: 23043160]
9. Lee-Kubli CA, Mixcoatl-Zecuatl T, Jolivald CG, Calcutt NA. Animal models of diabetes-induced neuropathic pain. *Curr Top Behav Neurosci*. 2014; 20:147–70. [PubMed: 24510303]
10. Morgenweck J, Abdel-Aleem OS, McNamara KC, Donahue RR, Badr MZ, Taylor BK. Activation of peroxisome proliferator-activated receptor gamma in brain inhibits inflammatory pain, dorsal horn expression of Fos, and local edema. *Neuropharmacology*. 2010; 58:337–45. [PubMed: 19891980]