Letter

Korean Diabetes J 2010;34:261-262
doi: 10.4093/kdj.2010.34.4.261
pISSN 1976-9180 · eISSN 2093-2650

kdj
KOREAN DIABETES JOURNAL

Effects of Rosiglitazone on Inflammation in Otsuka Long-Evans Tokushima Fatty Rats (*Korean Diabetes J* 2010;34:191-9)

Soo Jin Yang[1], Cheol-Young Park[2]

[1]Diabetes Research Institute, [2]Department of Endocrinology and Metabolism, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

Inflammation contributes to the development of type 2 diabetes and associated complications [1]. The inflammatory pathways activated by metabolic stress promote the secretion of pro-inflammatory cytokines and attract immune-inflammatory cells (e.g., macrophages and lymphocytes) into inflamed tissues. Subsequently, initiated inflammatory signals impair insulin action in insulin-responsive tissues such as the liver and skeletal muscles, inducing systemic insulin resistance throughout the body.

Thiazolidinediones (TZD), which are used as anti-diabetic drugs, are agonists for peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear transcription factor primarily involved in insulin action, lipid and glucose metabolism and energy homeostasis [2,3]. Several lines of evidence indicate that TZD can improve inflammation in peripheral tissues including muscle via the inhibition of specific pro-inflammatory signaling pathways (e.g., inhibitors of kappa B kinase beta/nuclear factor-kappa B [NF-κB]) [4-6], but the anti-inflammatory effects of TZD on skeletal muscle have not been extensively investigated.

The June issue of *Korean Diabetes J* included an important study by Lee et al. [7] on the effect of rosiglitazone (RGZ) on skeletal muscle inflammation in a rat model of moderate obesity and type 2 diabetes. The authors used Otsuka Long-Evans Tokushima Fatty (OLETF) rats as a rodent model of type 2 diabetes and demonstrated that RGZ administration results in the attenuation of diabetes and skeletal muscle inflammation. Interestingly, skeletal muscle inflammation was shown to be attenuated by the inhibition of two inflammatory pathways, ERK1/2 and NF-κB. We fully agree that RGZ improves insulin resistance in part due to anti-inflammatory effects in skeletal muscle as well as other peripheral tissues, and that the anti-inflammatory effects of RGZ are likely mediated by the suppression of pro-inflammatory cytokines and pathways. However, one issue that attracted our attention is that plasma free fatty acid (FFA) concentrations were lower in OLETF rats than in Long-Evans Tokushima Otsuka (LETO) rats although there is no alteration in plasma FFAs with RGZ treatment in OLETF rats. The current knowledge, as reflected in previous publications regarding skeletal muscle inflammation, is that excessive influx of FFA into skeletal muscle leads to pro-inflammatory states in skeletal muscle that in turn exert detrimental effects on insulin sensitivity [8,9]. Without the excessive influx of FFA from the systemic circulation into skeletal muscle, it is unclear what triggers the pro-inflammatory state in obese and insulin resistant OLETF rats. There may be a possible explanation that systemic glucose toxicity in OLETF rats can induce pro-inflammatory states regardless of the absence of excessive FFA influx. To explain this, it would be helpful to analyze other lipid profiles such as triglycerides and total cholesterol. With respect to no significant effects on homeostasis model assessment-insu-

Corresponding author: Cheol-Young Park
Department of Endocrinology and Metabolism, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 108 Pyeong-dong, Jongno-gu, Seoul 110-746, Korea
E-mail: cydoctor@chol.com

lin resistance (HOMA-IR) and HOMA-β (HOMA beta cell function) values, the RGZ-mediated improvement in plasma glucose and insulin was enough to confirm the anti-diabetic effect of RGZ because HOMA-IR and HOMA-β are not validated to assess insulin sensitivity and beta-cell function in a rodent model.

The study by Lee et al. showed that RGZ attenuated the detrimental positive feedback cycle between uncontrolled pro-inflammatory states and hyperglycemia, resulting in the improvement in diabetes and skeletal muscle inflammation. Additional studies are needed to understand the mechanisms by which RGZ contributes to the improvement of skeletal muscle inflammation, especially to identify main regulatory pathways for anti-inflammatory effects of RGZ on skeletal muscles. In addition to confirming previous observations, we believe that the study by Lee et al. extends our understanding about RGZ's anti-inflammatory actions and its contribution to the improvement in insulin resistance and diabetes.

REFERENCES

1. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116:1793-801.
2. Olefsky JM. Treatment of insulin resistance with peroxisome proliferator-activated receptor gamma agonists. J Clin Invest 2000;106:467-72.
3. Ferre P. The biology of peroxisome proliferator-activated receptors: relationship with lipid metabolism and insulin sensitivity. Diabetes 2004;53 Suppl 1:S43-50.
4. Remels AH, Langen RC, Gosker HR, Russell AP, Spaapen F, Voncken JW, Schrauwen P, Schols AM. PPARgamma inhibits NF-kappaB-dependent transcriptional activation in skeletal muscle. Am J Physiol Endocrinol Metab 2009;297:E174-83.
5. Mohanty P, Aljada A, Ghanim H, Hofmeyer D, Tripathy D, Syed T, Al-Haddad W, Dhindsa S, Dandona P. Evidence for a potent antiinflammatory effect of rosiglitazone. J Clin Endocrinol Metab 2004;89:2728-35.
6. Jiang C, Ting AT, Seed B. PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. Nature 1998;391:82-6.
7. Lee JW, Nam-Goong IS, Kim JG, Yun CH, Kim SJ, Choi JI, Kim YI, Kim ES. Effects of rosiglitazone on inflammation in Otsuka Long-Evans Tokushima Fatty rats. Korean Diabetes J 2010;34:191-9.
8. Krebs M, Roden M. Molecular mechanisms of lipid-induced insulin resistance in muscle, liver and vasculature. Diabetes Obes Metab 2005;7:621-32.
9. Delarue J, Magnan C. Free fatty acids and insulin resistance. Curr Opin Clin Nutr Metab Care 2007;10:142-8.