RXR agonists inhibit high glucose-induced upregulation of inflammation by suppressing activation of the NADPH oxidase-nuclear factor-κB pathway in human endothelial cells

R.B. Ning¹*, J. Zhu¹*, D.J. Chai², C.S. Xu³, H. Xie³, X.Y. Lin³, J.Z. Zeng⁴ and J.X. Lin²

¹The First Clinical Medical College, Fujian Medical University, Fuzhou, Fujian, China
²Cardiovascular Department, The First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian, China
³Echocardiological Department, The First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian, China
⁴School of Pharmaceutical Sciences and Institute for Biomedical Research, Xiamen University, Xiamen, China

*These authors contributed equally to this study.

Corresponding authors: D.J. Chai / J.X. Lin
E-mail: dajunchai@126.com / jinxiulin368@126.com

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ABSTRACT. An inflammatory response induced by high glucose is a cause of endothelial dysfunction in diabetes and is an important contributing link to atherosclerosis. Diabetes is an independent risk factor of atherosclerosis and activation of retinoid X receptor (RXR) has been shown to exert anti-atherogenic effects. In the present study, we examined the effects of the RXR ligands 9-cis-retinoic acid (9-cis-RA) and SR11237 on high glucose-induced inflammation in human umbilical endothelial vein endothelial cells (HUVECs) and explored the potential mechanism.
Our results showed that the inflammation induced by high-glucose in HUVECs was mainly mediated by the activation of nuclear factor-B (NF-κB). High glucose-induced expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) were in comparison, significantly decreased by treatment with RXR. The effect of RXR agonists was mainly due to the inhibition of NF-κB activation. Using pharmacological inhibitors and siRNA, we confirmed that nicotinamide adenine dinucleotide phosphate (NADPH) oxidase was an upstream activator of NF-κB. Furthermore, RXR agonists significantly inhibited high glucose-induced activation of NADPH oxidase and significantly decreased the production of reactive oxygen species (ROS). To explore whether the rapid inhibitory effects of RXR agonists were in fact mediated by RXR, we examined the effect of RXR downregulation by RXR siRNA. Our results showed that RXR siRNA largely abrogated the effects of RXR agonists, suggesting the requirement of RXR expression. Therefore, we have shown that RXR is involved in the regulation of NADPH oxidase- NF-κB signal pathway, as the RXR ligands antagonized the inflammatory response in HUVECs induced by high glucose.

**Key words:** Retinoid X receptor; Endothelial cells; High glucose; NF-κB; NADPH oxidase; Inflammation