F-D2

# 당뇨병성 혈관합병증에서 대식세포 활성화의 조절자로서 베타2 아드레날린 수용체 항진제의 역할

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# Beta2 Adrenergic Receptor Agonists: Novel Regulator of Macrophage Activation in Diabetes

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Activation of macrophages is increased in diabetes and correlated with the onset and progression of vascular complications. To identify drugs of potential use in targeting macrophage activation, we developed a cell-based assay and undertook screening for anti-inflammatory effect in a 1,040 compound library. Beta2 adrenergic receptor (β2AR) agonists were identified as the most potent inhibitor of phorbol myristate acetate or LPS-induced TNF-αproduction in rat bone marrow (BM)-derived macrophages. In PBMC isolated from streptozotocin-induced diabetic rats, β2AR agonists inhibited diabetes-induced TNF-αproduction, which was prevented by cotreatment with selective β2AR blockade. To clarify the mechanisms, THP-1 cells and BM-derived macrophages were exposed to high glucose (HG). HG reduced β-arrestin2, a negative regulator of NFκB activation, and its interaction with IκBα, which subsequently enhanced phosphorylation and ubiquitination of IκBαand activation of NFκB. Beta2AR agonists enhanced β-arrestin2 and induced interaction with IκBα, leading to down-regulation of NFκB. Beta-arrestin2-specific siRNA reversed the ability of β2AR agonists to inhibit NFκB activation and inflammatory cytokine production. In vivo, treatment of Zucker diabetic fatty (ZDF) rats with β2AR agonist for 12 weeks attenuated activation of peripheral and BM mononuclear cells and pro-inflammatory and pro-fibrotic responses in the kidneys and the heart. These data suggest that β2AR agonists have anti-inflammatory properties and might therefore have protective effects against diabetic renal and cardiovascular complications.

**Key Words:** 당뇨병성 혈관합병증, 대식세포, 베타2 아드레날린
Diabetic vascular complications, Macrophage, Beta2 adrenergic