Gambro 신진연구비

# Cinacalcet Activates AMPK and Ameliorates Diabetic Nephropathy through Intracellular Ca++-CaMMKβ Activation

Ji Hee Lim, Hyung Wook Kim, Min Young Kim, Yaeni Kim
Yong-Soo Kim, Yoon Sik Chang, Cheol Whee Park

Department of Internal Medicine, College of Medicine, The Catholic University of Korea

In cardiovascular system, the Calcium-sensing receptor(CaSR) simulates the production of NO in the endothelial cells. A decrement in NO bioavailability associated with AMPK inactivation and increased generation of reactive oxygen species are critical to the pathogenesis of diabetic vascular complications. Therefore, we evaluated the renoprotective effect of cinacalcet on glucotoxicity through AMP-protein kinase (AMPK)-eNOS-NO pathway in diabetic nephropathy in db/db mice and human glomerular endothelial cells (HGECs).

Male C57 BLKS db/db mice and db/m controls at 8 weeks of age were divided to receive either a regular diet chow or a diet containing cinacalcet (10 mg/kg; n=8, respectively). Mice were followed for 12 weeks and were evaluated for renal functions, pathologic phenotypes, and AMPK-eNOS-NO pathway.

Cinacalcet ameliorated albuminuria in db/db mice without influencing the changes in blood glucose and Ca++ concentrations. The mesangial area expansion and inflammatory cell infiltration in the glomerulus were observed in db/db mice, which were all restored by cinacalcet treatment. Cinacalcet increased expression of CaSR, phosphorylation of CaMMKβ and LKB1 and subsequent AMPK activation, which in turn activated PGC-1α and phospho-Ser1177 eNOS-NO. As a result, an increase in the ratio of Bcl-2/Bax in renal cortex and decrease in urinary 8-hydroxy-deoxyguanosin and isoprostane concentrations enhanced the expression of superoxide dismutase; SOD1 and SOD2. In cultured HGECs, cinacalcet decreased oxidative stress and apoptosis by increasing intracellular Ca++ and by enhancing phosphorylation of CaMMKβ, LKB1 and AMPK, which were associated with an increase in the phosphorylation of eNOS-NO as well.

In conclusion, the results suggest that cinacalcet improves glucotoxicity through an increase in intracellular Ca++ and subsequent activation of the CaMKKβ-LKB1-AMPK signaling in the kidney, especially GECs, and may be a potential therapeutic modality for type 2 diabetic nephropathy.

**Key Words:** Cinacalcet, Diabetic Nephropathy, Calcium-sensing receptor