TNF- α converting enzyme (TACE) inhibitor prevents insulin resistance and diabetic peripheral neuropathy

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Background: Tumor necrosis factor- α (TNF- α) converting enzyme (TACE/ADAM17) is a key sheddase that releases TNF- α from its inactive precursor and is thought as a new drug target to inhibit TNF- α production. In the present study, pharmacological effects of a novel TACE selective inhibitor, JTP-96193, on type 2 diabetes and its complication (diabetic peripheral neuropathy; DPN) were examined.

Methods: Enzyme inhibitory activity of JTP-96193 on TACE and other ADAMs were measured in *in vitro*. Fat-induced obese mice and diabetic KK-Ay mice were used to evaluate the effect of JTP-96193 on insulin resistance. Finally, streptozotocin (STZ)-induced diabetic mice were treated JTP-96193 and sciatic nerve conduction velocities (MNCV) were measured to evaluate the effect on DPN.

Results: JTP-96193 selectively inhibited human TACE with IC₅₀ value of 5.4 nM. In mice model of obesity and diabetes, JTP-96193 reduced the TNF- α release and increased glucose oxidation respectively in fat tissue. JTP-96193 prevented delay of sciatic MNCV without any effects on blood glucose or insulin levels in STZ-induced diabetic mice.

Conclusion: TACE inhibitor is effective on type 2 diabetes and DPN independent from glucose lowering effect.