Anti-diabetic and anti-obesity effects of the allosteric PTP1B inhibitor KY-226 via insulin and leptin signal enhancement

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Background: PPAR γ agonists have been used as insulin sensitizers for the treatment of type 2 diabetes; however, they also exert a number of adverse effects. Therefore, the development of PPAR γ -independent insulin sensitizers is desired. Since protein tyrosine phosphatase 1B (PTP1B) is a negative regulator of insulin and leptin signaling, PTP1B inhibitors have potential as anti-diabetic and anti-obesity drugs. We previously reported the novel non-competitive allosteric PTP1B inhibitor 4-(biphenyl-4-ylmethylsulfanylmethyl)-N-(hexane-1-sulfonyl)benzamide (KY-226). In the present study, we pharmacologically characterized KY-226 and investigated its effects on experimental diabetes and obesity.

Methods: The PTP1B inhibitory activity, PPAR γ agonist activity, and effects of KY-226 on adipocyte differentiation in 3T3-L1 cells and insulin-induced phosphorylation in HepG2 cells were examined. The effects of KY-226 on diabetes via insulin signal enhancement in *db/db* mice on obesity and via leptin signal enhancement in diet-induced obesity (DIO) mice were also investigated.

Results: KY-226 inhibited PTP1B activity ($IC_{50}=0.28 \mu M$) and potentiated the insulin-induced phosphorylation of insulin receptor (IR) in HepG2 cells. KY-226 did not exhibit PPAR γ agonist activity and had no significant effects on adipocyte differentiation, whereas the PPAR γ agonist pioglitazone significantly enhanced it. In *db/db* mice, KY-226 reduced plasma glucose levels at 30 mg/kg/day (p.o., 4 weeks) and TG and HbA1c levels at 10 and 30 mg/kg/day without increasing body weight, while pioglitazone exerted similar diabetic effects with elevations in body weight. In the oral glucose tolerance test, KY-226 significantly decreased elevated plasma glucose levels. KY-226 enhanced the insulin-induced phosphorylation of IR and Akt in the liver and femoral muscle. In DIO mice, KY-226 decreased total food consumption at 60 mg/kg/day, and body weight gain and fat volume gain at 30 and 60 mg/kg/day. KY-226 also potentiated the leptin-induced phosphorylation of STAT3 in the hypothalamus.

Conclusions: These results demonstrate that KY-226 exerts anti-diabetic and anti-obesity effects by enhancing insulin and leptin signaling, respectively, without increasing body weight. Thus, KY-226 is a promising candidate for an efficacious and safe anti-diabetic drug with anti-obesity effects.