161-LB

Effects of DA-1241, A Novel GPR119 Agonist, on Lipid Control in Disease Models Mediated by Regulating an AMPK/SREBP1c Signaling Path

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Abstract

DA-1241 is a novel, potent and selective GPR119 agonist under early clinical development, which was reported to have sustained anti-diabetic effects in diabetic animal models. The purpose of the herein study is to investigate the lipid-lowering effects of DA-1241 in disease models and to explore the underlying mechanisms.
Chronic administration of DA-1241 completely normalized the plasma triglycerides (TG) levels and thereby decreased hepatic TG accumulation in dyslipidemic mice. The lipid-lowering effect of DA-1241 was comparable to GSK-1292263A and synergistically augmented by combination therapy with sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, through enhancing the incretin effects. DA-1241 treatment also significantly alleviated plasma cholesterol levels in a same mice model and attenuated the disease progression with a comparable efficacy to atorvastatin in high cholesterol-fed rats. When DA-1241 was acutely given to normal mice by oral gavage prior to corn oil loading, the postprandial TG excursion was dose-dependently suppressed, which seemed to partly contribute to the chronic lipid control in high fat-fed mice. In cell-based experiments using human hepatoma cells, DA-1241 treatment activated AMP-activated protein kinase (AMPK), increased phosphorylation of sterol regulatory element-binding transcription factor (SREBP)1c, an inhibitory form of SREBP1c, decreased total SREBP1c expression, and thereby suppressed the downstream lipogenic signals. Moreover, we found that DA-1241 modulated the protein expression of SREBP1c and phospho-p38 kinase levels altered by a liver X receptor (LXR) agonist in an opposite way.

Background

- GPR119 is a early responder to intraduodenal lipid as a fat sensor (*Hansen et al.*, 2012; *Cvijanovic et al.*, 2017)
- GPR119 mediates postprandial lipid-lowering via incretin actions (*Bahirat et al.*, 2017).
- GPR119 activation alleviates hepatic steatosis by inhibiting SREBP-1-mediated *de novo* lipogenesis in hepatocytes (*Yang et al.*, 2016).

Methods

- ***Animal studies***
  - High fat diet (HFD)/streptozotocin (STZ)-induced hypertriglyceridemic mice
  - High fat/high fructose diet (HFHFrD)-fed dyslipidemic mice
  - High cholesterol diet (HCD)-fed rats
  - Acute triglyceride tolerance test in ICR mice
- ***MoA in human hepatoma cell line (HepG2)***

Results

- ***Treatment effects in pre-established dyslipidemic mice***

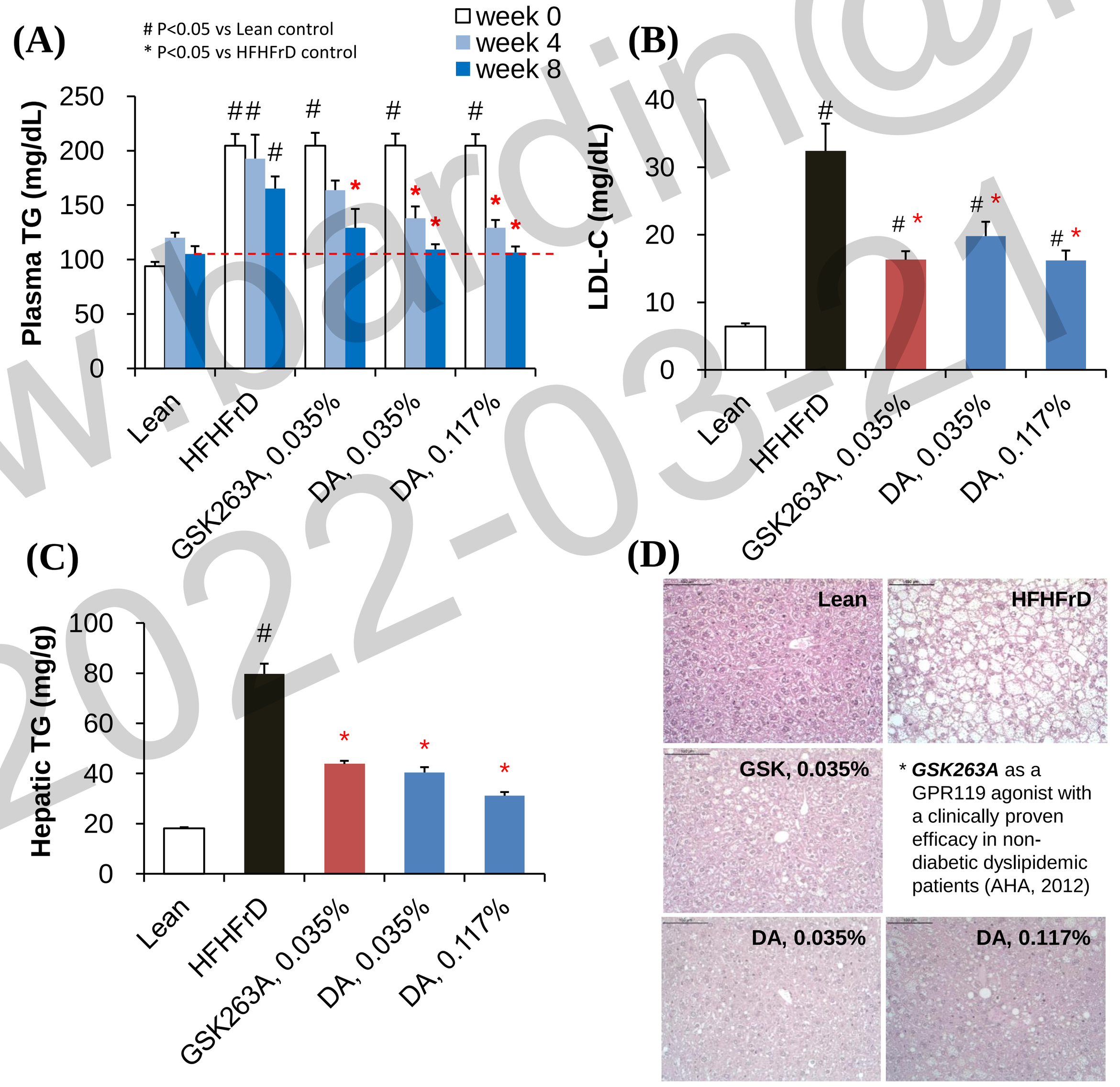

Figure 1. *In addition to plasma TG (A) and LDL-choleterol (B) levels, hepatic TG accumulation was assessed by both biochemical (C) and histological (D; HE staining) methods after 8-week treatment in HFHrD-induced pre-established dyslipidemic mice. These results suggested therapeutic potential for dyslipidemia.*

Results

- ***Synergistic augmentation of lipid-lowering efficacy by combination with a DPP4 inhibitor***

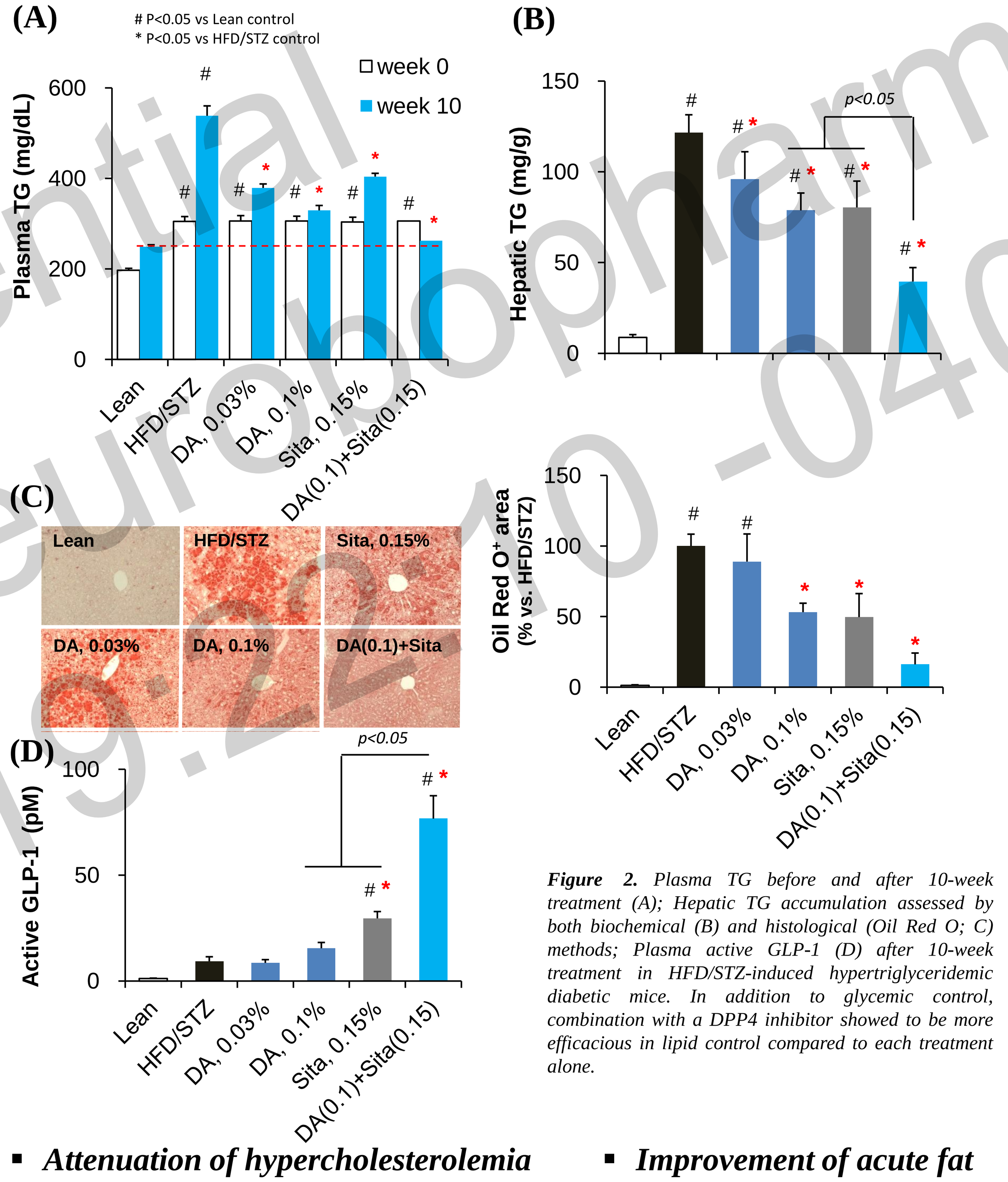

Figure 2. *Plasma TG before and after 10-week treatment (A); Hepatic TG accumulation assessed by both biochemical (B) and histological (Oil Red O; C) methods; Plasma active GLP-1 (D) after 10-week treatment in HFD/STZ-induced hypertriglyceridemic diabetic mice. In addition to glycemic control, combination with a DPP4 inhibitor showed to be more efficacious in lipid control compared to each treatment alone.*

- ***Attenuation of hypercholesterolemia progression in HCD-fed rats***

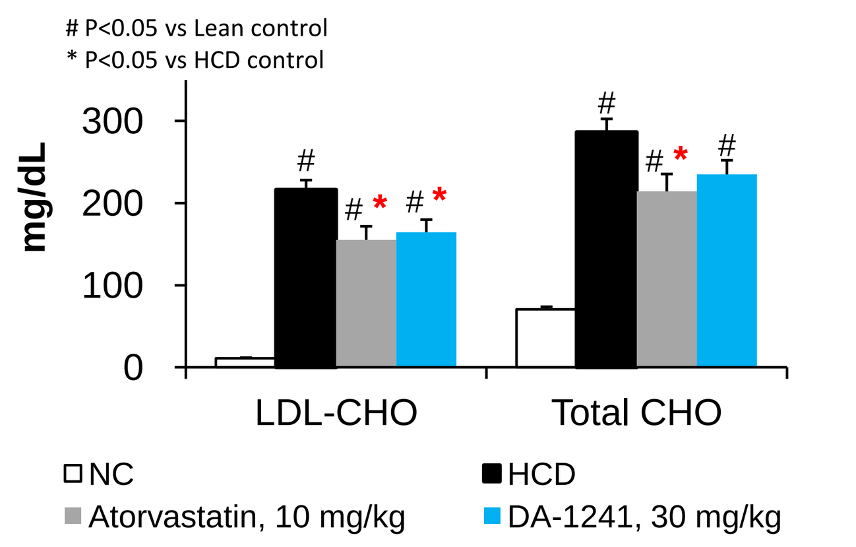

Figure 3. *Plasma cholesterol levels after 1-week treatment by oral gavage in SD rats fed on a HCD*

- ***Improvement of acute fat tolerance in normal mice***

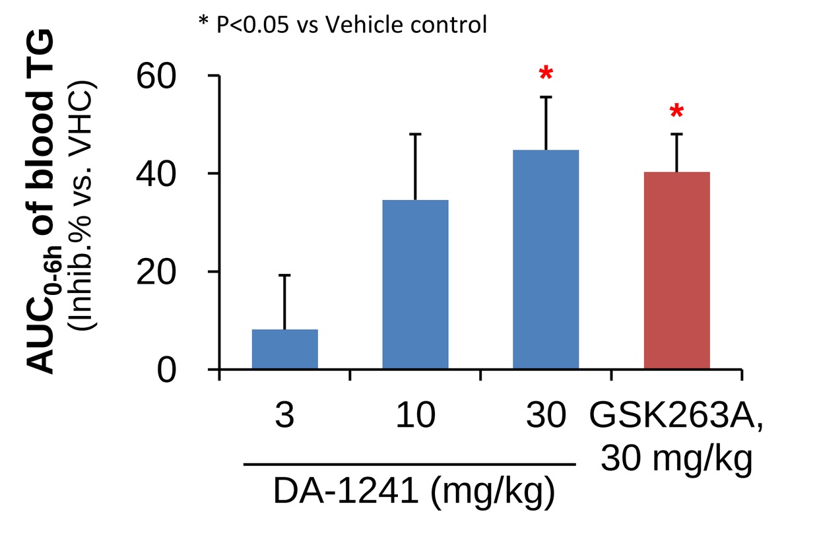

Figure 4. *AUC inhibition of blood triglycerides after single oral administration followed by corn oil loading in ICR mice*

Results

- ***DA-1241 suppressed de novo lipogenesis via regulating AMPK/SREBP1c signaling***

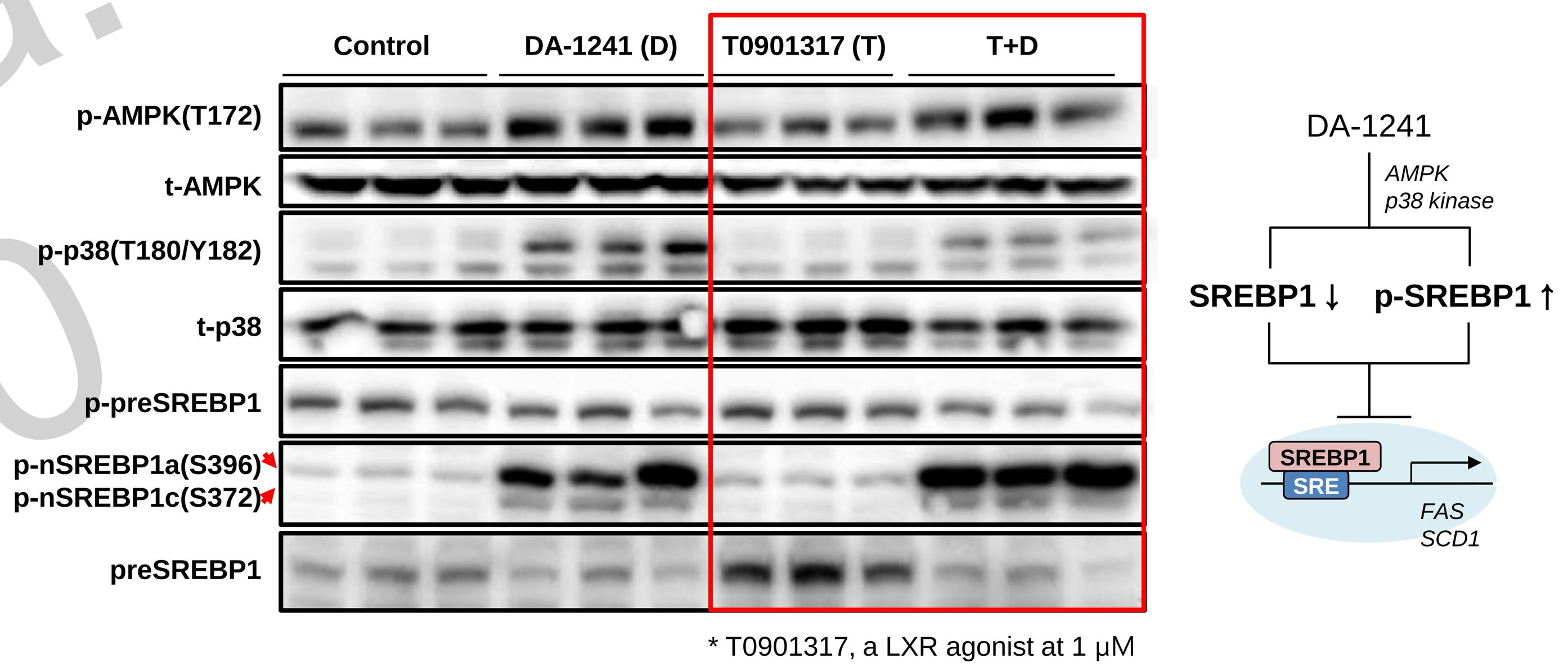

Figure 5. *DA-1241 activated AMPK and p38 kinase, then increased phosphorylation of nuclear form SREBP1, thereby augmenting proteosomal degradation of SREBP1. Meanwhile, DA-1241 suppressed the SREBP1 protein expression induced by LXR activation.*

Conclusion

Our findings suggest;

i) The therapeutic potential of DA-1241 for the treatment of dyslipidemia

ii) DA-1241 can be a best combination partner for DPP4 inhibitors with further metabolic benefits other than glucose control via augmenting incretin effects

iii) The further elucidation for the potential underlying mechanisms of GPR119 agonist in lipid control.

** DA-1241 is currently under early clinical development.*

References

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