

The Reason is Still Unclear

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Type 2 diabetes mellitus (T2DM) is associated with a marked increase in the risk of atherosclerotic cardiovascular disease (ASCVD). High concentrations of low-density lipoprotein (LDL) cholesterol are a major modifiable risk factor for ASCVD, and statins are highly effective therapies for reducing LDL cholesterol levels in T2DM patients. However, residual cardiovascular risk remains, and many patients cannot tolerate statins. Therefore, antidiabetic agents which also reduce LDL cholesterol may be clinically useful.

Anagliptin, a dipeptidyl peptidase-4 inhibitor, has been shown to decrease LDL cholesterol levels. In the Randomized Evaluation of Anagliptin versus Sitagliptin On low-density lipoprotein cholesterol in diabetes (REASON) trial, anagliptin reduced LDL cholesterol to a greater extent than sitagliptin, another DPP-4 inhibitor, among T2DM patients who were receiving statin therapy.

In this issue of the journal, Furuhashi *et al.* investigated the effect of treatment with anagliptin or sitagliptin on serum proprotein convertase subtilisin/kexin type 9 (PCSK9) concentration as a sub-analysis of the REASON trial¹⁾. They found that PCSK9 level was significantly increased by sitagliptin treatment and it tended to be increased, but not significantly, by anagliptin. Interestingly, anagliptin decreased LDL cholesterol by approximately 5% independent of hemoglobin A1c control. As serum PCSK9 increase by anagliptin was less than that by sitagliptin, the authors speculated that anagliptin possibly reduces LDL cholesterol by suppressing excess statin-mediated PCSK9 induction and subsequent degradation of the LDL receptor.

In my view, these findings and this speculation are interesting, but also raise critical unanswered questions. First, the reason why PCSK9 induction by

anagliptin is less than that by sitagliptin is still unclear. In addition, as serum PCSK9 levels tended to be increased by anagliptin, mechanisms by which anagliptin reduces serum LDL cholesterol remain to be solved. Is there anything else to investigate? (Fig. 1)

It has been reported that statins increase plasma PCSK9 levels and decrease plasma sortilin levels and statin-induced PCSK9 changes were associated with changes in plasma sortilin²⁾. Sortilin colocalizes with PCSK9 in the trans-Golgi network and facilitates its secretion from primary hepatocytes. Furthermore, circulating PCSK9 and sortilin were positively correlated in a human cohort of healthy individuals, suggesting that sortilin is involved in PCSK9 secretion in humans³⁾. Since evidence for an association between sortilin and plasma LDL cholesterol levels is not convincing⁴⁾, investigation of the effect of anagliptin and other DPP-4 inhibitors on plasma sortilin levels and hepatic sortilin expression may give a new insight into the relationship between sortilin and LDL cholesterol. In addition, the effect of DPP-4 inhibitors on PCSK9 excretion also needs to be addressed. Besides PCSK9, inducible degrader of the LDL receptor (IDOL), a target of liver X receptor (LXR), also promotes degradation of the LDL receptor. However, the effect of anagliptin on the LXR-IDOL axis is unknown.

As Furuhashi *et al.* stated in the Discussion section, it has been reported that anagliptin reduced serum lathosterol, a cholesterol synthesis marker. However, another study reported that anagliptin did not change serum lathosterol levels. Therefore, clear-cut mechanisms by which anagliptin, but not sitagliptin, reduces serum LDL cholesterol level remain to be worked out. From a different viewpoint, investigation of the effects of anagliptin and DPP-4 inhibitors on the number and/or size of LDL particles may shed light on mechanisms underlying LDL cholesterol reduction by anagliptin.

Although we should recognize that the REASON

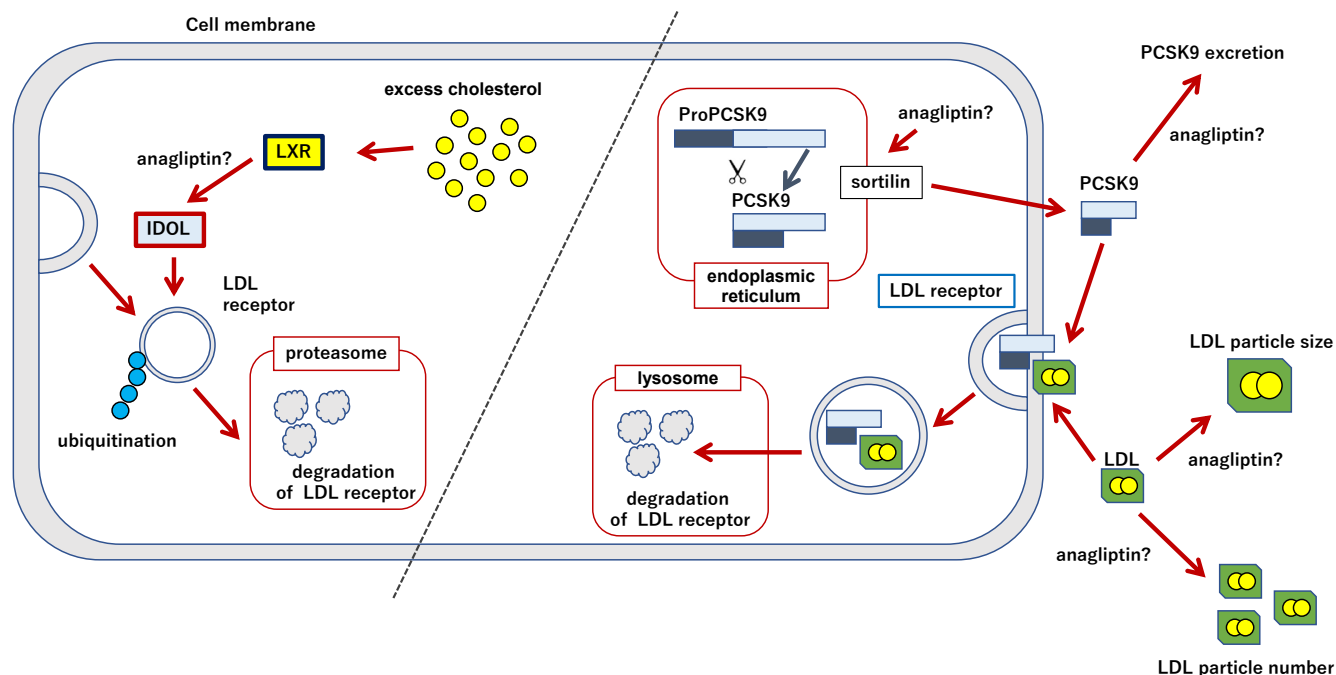


Fig. 1. Other possible mechanisms underlying serum LDL cholesterol reduction by anagliptin

study was funded by Kowa, Furuhashi et al clearly demonstrated that anagliptin reduced LDL cholesterol in statin-treated T2DM patients, and PCSK9 induction by anagliptin was less than that by sitagliptin. Additionally, serum PCSK9 level was independently associated with platelet count and triglycerides concentration. As PCSK9 is an important therapeutic target among statin-treated patients, the combination of statin and anagliptin may be a favorable therapeutic option in dyslipidemia with T2DM. However, the reason why anagliptin reduces LDL cholesterol is still unclear.

Conflicts of Interests

Masatsune Ogura has received honoraria from Amgen and Astellas Pharma Inc.

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