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LETTER

Cholesterol toxicity in pancreatic islets from LDL receptor-deficient mice

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Abbreviation
ABCA1 ATP-binding cassette transporter A1

To the Editor: In a recent issue of *Diabetologia*, Kruit and colleagues presented an article regarding the role of cholesterol-induced impairment of beta cell function in mice [1]. The authors found that in $Ldlr^{-/-}$ knockout mice, which lack the LDL receptor, islet cholesterol content was normal despite moderate hypercholesterolaemia, and in the presence of very high plasma cholesterol levels induced by a Western-style diet, glucose-stimulated insulin secretion was not reduced. On the other hand, $Ldlr^{-/-}$ knockout mice with beta cell-specific ATP-binding cassette transporter A1 (ABCA1) deficiency showed increased islet cholesterol content and beta cell dysfunction, suggesting that cholesterol efflux through ABCA1 is the critical regulator of islet cholesterol content and beta cell function. In their discussion of the results, the authors claim that $Ldlr^{-/-}$ knockout mice are protected from the deleterious effects of hypercholesterolaemia.

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Almost simultaneously, our group published results showing that islets from $Ldlr^{-/-}$ knockout mice have increased cholesterol content and impaired beta cell function [2]. We reported that glucose-stimulated insulin secretion is reduced in $Ldlr^{-/-}$ mice, and that the dose–response curve is shifted to the right, indicating that islets from these mice are less sensitive to glucose. The dynamic analysis of insulin secretion showed that in $Ldlr^{-/-}$ mice both first- and second-phase secretion in response to a 11 mmol/l glucose challenge is reduced, even though there is no alteration in islet insulin content. Such results are associated with reduced glucose uptake and oxidation by $Ldlr^{-/-}$ islets. This impairment is not related to altered islet or beta cell mass, and is sufficient to elicit glucose intolerance in the absence of peripheral insulin resistance [2]. Using the same technique as Kruit et al. [1], and in contrast to their findings, we observed a significant increase (32%) in islet cholesterol content in $Ldlr^{-/-}$ mice [2]. Perhaps a large data variation in their islet cholesterol results confounded statistical analyses. Our results showed that elevated islet cholesterol was responsible for beta cell dysfunction, since its depletion by methyl-β-cyclodextrin treatment corrected glucose stimulated insulin secretion. Islet cholesterol elevation is likely the result of a gradient-driven cholesterol flow from the plasma to the cell membranes associated with de novo cholesterol synthesis in $Ldlr^{-/-}$ islet.

Kruit and colleagues [1] showed in a very elegant manner that an in vivo process of islet cholesterol removal (cholesterol efflux through ABCA1) is relevant for maintaining cell cholesterol homeostasis and beta cell function. Thus, both works are in agreement that excess cholesterol impairs while removal of islet cholesterol improves insulin secretion. However, we provided data demonstrating that

the absence of the LDL receptor increased islet cholesterol content and did not protect beta cells against hypercholesterolemia [2], as proposed by Kruit and colleagues [1]. Unfortunately, they did not measure insulin secretion or glucose tolerance in chow-fed *Ldlr*$^{-/-}$ mice as we did. Their studies in these mice were performed only after long periods of a high-fat Western-type diet, which is well known to compromise both insulin secretion and glucose tolerance [3]. Under these conditions they showed that ABCA1 transporters have a protective role in beta cell functioning. Conversely, our group demonstrated that, in the absence of metabolic confounding factors induced by unbalanced diets or obesity, hypercholesterolaemia induced by a lack of the LDL receptor has a deleterious effect on glucose homeostasis and beta cell function [2].

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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