



Title	Plasma lipocalin-2 concentration is related to blood pressure and is increased in hypertension
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Objective: Type 2 diabetes is characterised by peripheral insulin resistance and defective insulin secretion from pancreatic islets. Our previous study demonstrated that the adaptor protein APPL1 positively regulates insulin actions in liver and endothelium. In this study, we aimed to investigate whether or not APPL1 regulates pancreatic beta-cell functions using a knockout (KO) mouse model.

Methods: APPL1 KO mice and its wild-type littermates were subjected to high-fat diet feeding for 24 weeks. The glucose metabolism and beta-cell functions were examined in these mice.

Results: APPL1 was abundantly expressed in mouse pancreatic beta cells, but its expression was significantly decreased in obese and diabetic conditions. Genetic ablation of APPL1 resulted in glucose intolerance due to decreased glucose-stimulated insulin secretion in mice. Ex-vivo study showed that pancreatic islets lack of APPL1 exhibited blunted glucose- and potassium-stimulated insulin secretion accompanied by a marked reduction in expression of the exocytotic machinery SNARE proteins and docked insulin granules, while glucose metabolism and calcium mobilisation remained unchanged. On the other hand, these defects were rescued by adenovirus-mediated expression of APPL1 or a constitutively active form of Akt. Furthermore, co-immunoprecipitation assay revealed that APPL1 interacted with syntaxin-1, a key molecule in SNARE protein complex, upon glucose stimulation. Knockdown of APPL1 expression reduced the complex formation of SNARE protein in beta cells, whereas overexpression of APPL1 enhanced this complex formation. Taken together, these results suggest that APPL1 regulates protein expression as well as complex formation of SNARE proteins, thereby controlling insulin secretion in beta cells.

Conclusion: Our study establishes a new role for APPL1 in beta-cell functions, and suggests that the downregulation of APPL1 may contribute to impaired insulin secretion in type 2 diabetes.

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Introduction: Lipocalin-2 is secreted by adipocytes and is upregulated in obesity. As obesity is known to be a cause of hypertension, we investigated whether the plasma level of lipocalin-2 is related to blood pressure and hypertension.

Methods: The plasma concentration of lipocalin-2 was measured by immunoassay in 1925 subjects of the Hong Kong Cardiovascular Risk Factor Prevalence Study (CRISPS). Blood pressure was measured after prolonged resting by a trained nurse manually using a calibrated sphygmomanometer three times at 5-minute intervals.

Results: Plasma lipocalin-2 level was higher in men than in women (median [IQR] 37.7 [30.5-47.9] vs 31.6 [25.4-40.4], $P < 0.001$). It was significantly related to age ($r = 0.15$, $P < 0.001$) and systolic blood pressure ($r = 0.15$, $P < 0.001$). In women but not in men, it was also significantly related to waist circumference ($r = 0.16$, $P < 0.001$), body mass index ($r = 0.09$, $P = 0.004$), diastolic blood pressure ($r = 0.14$, $P < 0.001$) and fasting plasma glucose ($r = 0.089$, $P = 0.004$). Plasma lipocalin-2 level was significantly higher ($P < 0.001$ adjusted for age) in hypertensive men and women (median [IQR], 41.1 [31.7-53.0] and 36.5 [27.5-50.1]) compared to normotensive men and women (36.9 [29.6-45.6] and 30.9 [25.2-38.3]).

Conclusion: Plasma lipocalin-2 concentration is related to systolic blood pressure, and is higher in men and in people with hypertension. Lipocalin-2 may be involved in the pathogenesis of hypertension.

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