Significance of Feedback Inhibition of Insulin Secretion by Insulin in Healthy Non-obese Men

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Endogenous insulin secretion is suppressed during hyperinsulinemic euglycemic clamp, which is known as a feedback inhibition of insulin secretion (FI-IS) by insulin. Since FI-IS is impaired in obese subjects, inadequate FI-IS may partly contribute to enhanced insulin secretion seen in obesity with insulin resistance. However, significance of FI-IS in non-obese healthy subjects is unknown. To clarify the significance, we studied 49 non-obese healthy Japanese men. We evaluated steady state serum C-peptide (SSSC) and muscle insulin sensitivity (MIS) by hyperinsulinemic euglycemic clamp with tracer (insulin infusion rate = 20 mU/m² per min). We also measured intrahepatic lipid (IHL) by ¹H-MRS. Based on the median of SSSC, we divided the subjects into low FI-IS group and high FI-IS group and compared clinical parameters. While fasting C-peptide level was comparable between the groups, the SSSC was suppressed by 50% from baseline in the high FI-IS group (1.14 ± 0.39 to 0.57 ± 0.24 ng/mL, $p < 0.001$), but less suppressed in the low FI-IS group (1.34 ± 0.34 to 1.19 ± 0.24 ng/mL, $p = 0.054$). Although most of metabolic parameters such as fasting glucose, lipid levels and visceral fat volume were comparable between the groups, low FI-IS group showed IHL accumulation (3.0 ± 4.2 vs. $0.6 \pm 0.2\%$, $p = 0.04$) and impaired MIS (0.19 ± 0.04 vs. 0.28 ± 0.08 mg/kg FFM $\cdot$ min⁻¹ $\cdot$ μ U⁻¹ $\cdot$ mL, $p < 0.001$), compared with high FI-IS group. Consistently, we observed elevated AUC of insulin during 75 g-OGTT in low FI-IS group (6.6 ± 3.0 vs. 3.9 ± 2.0 μ U $\cdot$ min/mL $\cdot$ 10³, $p = 0.001$), while AUC of glucose was comparable. In conclusion, even in healthy non-obese men, subjects with inadequate FI-IS were existed and those were characterized by impaired MIS and hyperinsulinemia during OGTT. These data suggested that impaired FI-IS may be early change to maintain metabolic status through enhancing insulin secretion in the face of moderate muscle insulin resistance in healthy non-obese men.

Key words: feedback inhibition of insulin secretion, insulin resistance, hyperinsulinemia

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