Control/Tracking Number: 2013-A-3839-Diabetes
Activity: Abstract
Current Date/Time: 1/6/2013 4:32:12 PM

Features in subjects with increased fasting glucagon concentration after administration of a DPP-4 inhibitor

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Abstract:
Abnormal regulation of glucagon secretion is a feature of type 2 diabetes mellitus. Dipeptidyl peptidase 4 inhibitors (DPP4-Is) may ameliorate the glucagon regulation. After administration of a DPP4-I, however, an increased fasting glucagon conc. paradoxically has been observed in some patients. To identify the features in those subjects, we conducted oral glucose tolerance tests (OGTTs) in 10 such subjects (GlunH) and compared with 10 subjects without increased fasting glucagon conc (C). Total 20 patients (M/F:11/9, age=66±7 y.o., duration of diabetes=12±9 y., HbA1c=6.5±0.5%, BMI = 25±4kg/m^2) received OGTTs. 16 patients received sitagliptin, and four received vildagliptin. Insulin secretion and insulin sensitivity indices obtained from OGTT were compared with the fasting glucose, glucagon, insulin, C-peptide, and proinsulin conc. Basal glucagon conc. before administration of a DPP4-I was slightly lower in the GlunH group (72±17 vs 82±21pg/ml, NS), while glucagon levels were significantly increased at least two weeks after DPP4-I administration (by +16±9 vs -7±12 pg/ml). FPG was decreased in both groups (104±20 to 102±17 vs 131±29 to 116±23 mg/dl in C). Fasting insulin conc. was significant lower in the GlunH group (3.1±2.2 vs 4.7±2.5 microU/ml in C, $p<0.05$) before DPP4-I and slightly increased by 1.8±2.0 vs -0.1±1.0 microU/ml in C, p=NS. Matsuda index was significantly higher in the GlunH group (15.6±6.8 vs 7.7±2.9 in C, $p<0.01$), while insulinogenic index and HOMA-IR were not statistically different between the two groups (0.11±0.13 vs 0.10±0.09, and 0.9±.0.8 vs 1.6±0.6, respectively). Increment of glucagon conc. 30 min after an oral glucose intake was similar (4.0±13.0 vs 4.4 ±25.0 pg/ml in C, p=NS). In conclusion, paradoxical increase of fasting plasma glucagon conc. after DPP4-I administration coincides with increased whole body insulin sensitivity, suggesting the counteracting mechanism to avoid hypoglycemia by GLP-1 activation even during fasting state.