OBSERVATIONS

Incretin Effect of Glucagon-Like Peptide 1 Receptor Agonist Is Preserved in Presence of ABCC8/SUR1 Mutation in β-Cell

ABCC8/SUR1-activating mutations induce neonatal diabetes (1) or other diabetes (1–4). Sulfonylurea treatment is unsuccessful in 15% patients (2,3). Glucagon-like peptide 1 (GLP-1) enhances insulin secretion by activating diverse signaling pathways (4). This study aimed at exploring if the GLP-1 effect is retained when β-cell dysfunction is related to ABCC8 mutation.

Three informed patients were included after approbation by the local ethics committee. Patient 1 (38 years old, BMI 21 kg/m^2, 6.2% HbA_{1c}) and 2 (64 years old, BMI 27 kg/m^2, 7.4% HbA_{1c}) were diagnosed at ages 15 and 17 years as having type 1 diabetes and treated with insulin for years, until ABCC8 heterozygous mutation (c.1303T>C [p.Cys435Arg] and c.4139G>A [p.Arg1380His]) was discovered when a relative developed transient neonatal diabetes. They are now treated with glyburide. Patient 3 (63 years old, BMI 27 kg/m^2, 6.9% HbA_{1c}) is the sister of patient 2, diagnosed as having type 2 diabetes at age 24 years. She has the same mutation as her sister and is now treated with metformin, glimepiride, and exenatide.

Explorations were performed during a prolonged oral glucose tolerance test (OGTT; 75 g glucose) at 9 A.M., in three conditions. For the "no treatment condition," usual hypoglycemic treatment was stopped during 3 days. Diabetes was controlled with a subcutaneous insulin infusion (Lispro insulin; Eli Lilly, Indianapolis, IN), which was stopped 4 h before OGTT. For the "sulfonylurea condition," patients were taking their usual sulfonylurea treatment, and patient 3 stopped metformin and exenatide for 2 days. Patients were given 5 mg glyburide in addition to their usual sulfonylurea treatment 30 min before OGTT. For the "exenatide condition," usual hypoglycemic treatment was stopped for 4 days. Diabetes was controlled with a subcutaneous insulin infusion which was stopped 4 h before OGTT. Patients were given 10 μg exenatide (Byetta; Eli Lilly) 15 min before OGTT.

In absence of treatment, the three patients had a frank diabetic glycemic profile (time 120 min [T120] glycemic level: 18, 25, and 22 mmol/L) with a low maximal C-peptide level at T120 (1.1, 1, and 0.8 nmol/L, for normal range at fasting: 0.3 to 1.4 nmol/L). Under sulfonylurea, early C-peptide modestly increased in patient 1 (Δ 30 min 0.7 nmol/L), leading only in this patient to a moderate decrease of glycemic level. Surprisingly, sulfonylurea induced increase of glucagon level during OGTT. Conversely after injection of 10 μg exenatide, C-peptide level increased to a maximal level at T120 (1.7, 1.5, and 2.8 nmol/L), glucagon concentration was obviously decreased (Δ area under the curve glucagon −1, −1, −3.5 pg/mL/min), and glycemic level decreased to a minimal level at T120 (4, 9, and 5 mmol/L).

In conclusion, exenatide incretin effect was highly preserved despite ABCC8-related β-cell dysfunction. C-peptide concentration was increased at the same level as described in type 2 diabetes (5). This suggests that GLP-1 can facilitate the closure of the ATP-sensitive K^+ channel despite activating ABCC8 mutation. Overall exenatide induced a great improvement of post OGTT glycemic excursion. We suggest that patients with ABCC8 mutation who are not being successfully transferred from insulin to sulfonylurea could benefit from GLP-1 receptor agonist treatment, at least if they have some residual C-peptide secretion.

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DOI: 10.2337/dc12-0535

Acknowledgments—A.H. has received a grant from Eli Lilly. No other potential conflicts of interest relevant to this article were reported.

O.B. and C.B.-C. researched data, contributed to discussion, and reviewed the manuscript. F.C. researched data and wrote the manuscript. M.H., C.S.-M., A.A., and B.C. researched data. C.M. reviewed the manuscript. J.M.L. and A.H. researched data, contributed to discussion, and wrote the manuscript. A.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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