

OBSERVATIONS

**Incretin Effect of Glucagon-Like Peptide 1 Receptor Agonist Is Preserved in Presence of ABCC8/SUR1 Mutation in  $\beta$ -Cell**

**A**BCC8/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  $\beta$ -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<sup>2</sup>, 6.2% HbA<sub>1c</sub>) and 2 (64 years old, BMI 27 kg/m<sup>2</sup>, 7.4% HbA<sub>1c</sub>) 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<sup>2</sup>, 6.9% HbA<sub>1c</sub>) 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  $\mu$ g 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 ( $\Delta$  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  $\mu$ g 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 ( $\Delta$  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  $\beta$ -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<sup>+</sup> 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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