## Sera from Patients with Type 2 Diabetes Contain Agonistic Autoantibodies Against G Protein-Coupled Receptors

## To the Editor:

Agonistic autoantibodies (agAAB) directed against G protein-coupled receptors (GPCR) have been identified in dilated cardiomyopathy and different diseases with vascular complications, such as hypertension [1], preeclampsia [2] and vascular necrotic kidney graft rejection [3]. Notably, hypertension which dominantly associates with agAAB directed against the  $\alpha_1$ -adrenergic receptor  $(\alpha_1$ -AR) often combines with diabetes [1, 4]. Animal studies demonstrated that agAAB cause dilated cardiomyopathy and pre-eclampsia [5, 6]. Furthermore, the potential pathogenic role of  $\alpha_1$ -AR-activating agAAB was recently described in refractory hypertension [7]. agAAB preferentially target the second extracellular loop of the cognate GPCR and activate the receptor in a non-physiological manner by surpassing protective mechanisms of the target cell. Importantly, GPCR antagonists are able to abolish interaction of agAAB with the cognate receptor and may prevent the target tissue from damage [6].

In our laboratory we routinely analyse sera of patients for the presence of agAAB by means of a standardized bioassay based on the computer-assisted recording of the beating rate of spontaneously contracting cultured neonatal rat cardiomyocytes [8]. We studied the sera of 47 patients (13 females and 34 males) suffering from type 2 diabetes classified according to clinical criteria. Patients were on average (mean ± SD) 68 ± 10 years old with a body mass index mean of  $32.1 \pm 7.0 \text{ kg/m}^2$ , the duration of the disease was  $14 \pm 9$  years, and HbA<sub>16</sub> level was 7.4  $\pm$  1.5%. All patients were negative for  $\beta$ -cell autoantibodies. Immunoglobulin preparations of 25 sera out of 47 (53%) positively reacted in the bioassay. Next the agAAB spectrum of the 25 positive patients was further classified with respect to the targeted GPCR type by means of specific GPCR antagonists. We found that among these 25 sera, 9 (36%) contained agAAB directed against two types of GPCR, four (16%) were positive for agAAB directed against angiotensin II type 1 receptor and one (4%) was positive for  $\beta_1$ -adrenergic receptor interacting agAAB. Sixty-four per cent of the positive patients (16 out of 25) harboured agAAB directed against the  $\alpha_1$ -AR. Among these 16 patients, 75% had elevated blood pressure or were under treatment with antihypertensives. In a cohort of non-diabetic patients with

established therapy refractory hypertension, 21 sera out of 57 (37%) were found positive for the presence of agAAB. Twenty sera out of these 21 (95%) contained agAAB directed against the  $\alpha_1$ -AR. These data are consistent with a potential role of agAAB directed against the  $\alpha_1$ -AR in the development of hypertension [7].

Our results show for the first time the occurrence of potentially pathogenic agAAB directed against GPCR in patients suffering from type 2 diabetes. The presence of agAAB that mainly interact with the  $\alpha_1$ -AR suggests an increased risk of hypertension and vascular complications for diabetic patients. The association of agAAB with type 2 diabetes sheds new light on the therapeutic potential of clinically available GPCR antagonists. Furthermore, the role of intracellular calcium in the pathomechanism of agAAB strengthens the use of calcium antagonists [7]. Development of strategies to counteract agAAB role in type 2 diabetes is therefore important and relevant for the therapy of diabetic complications, in particular, high blood pressure and associated organ damages.

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