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NEW TARGETS FOR CLINICAL APPLICATION OF APHERESIS

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Abstract

Besides of the classical autoimmune diseases agonistic autoantibodies (agAAB) against adrenoceptors (AR) are associated with dilated cardiomyopathy (DCM), vascular necrotic renal graft rejection, preeclampsia and others. The agAAB do not act like physiological agonists only, moreover, they induce a chronic stimulation of receptors, which leads to fundamental change of intracellular calcium signaling. Until now there is no medical drug treatment available to stop the pathological function of agAAB. We present new data of agAAB against the α1-AR and its causative role in induction and maintaining vascular remodelling in vivo. The evidence of this agAAB to induce vascular remodelling and cerebrovascular obliteration defines them as target for therapeutic apheresis. The results open the opportunity for the treatment of patients with agAAB and serious diseases like vascular dementia alone and mixed forms with M. Alzheimer.

Keywords: adrenoceptor, agonistic autoantibodies, apheresis, vascular remodelling

I. INTRODUCTION

Agonistic autoantibodies (agAAB) stimulate G protein coupled receptors (GPCR) like physiological agonists, but they have several pathological properties. Since the detection of such AAB targeting the ß1-Adrenoceptor (ß1-AR) more as a dozen of diseases could be identified to be associated with agAAB beside of the classical autoimmune diseases. It could be demonstrated years ago that agAAB directed against the ß1-AR are causative for the development of dilated cardiomyopathy (DCM). Until today no medical drug treatment is available to stop the pathological action of agAAB. The removal of immunoglobulins from patient's plasma by immunoadsorption eliminates the agAAB and leads to a long lasting improvement of cardiac function (left ventricular ejection fraction), (1). Another important target for immunoadsorption/therapeutic apheresis seems to be agAAB directed against the α1-AR and ß2-AR (2). Here we summarize recent data of the E.R.D.E.-AAK-Diagnostik laboratory on agAAB screening in patients sera and on the mechanism of this agAAB against the α1-AR obtained at the cellular level as well as in animal experiments in vivo (1,2,4,5).

II. METHODOLOGY

The agAAB against AR were estimated in serum samples of patients with clinically diagnosed dementia (minimental state examination, MMSE 20-28). The serum samples were collected from patients of the Evangelisches Geriatriezentrum Berlin (EGZB, Head: Prof. Dr. Elisabeth-Steinhagen-Thiessen) with permission of the ethic commission of the Charité, Berlin. A bioassay using neonatal rat cardiomyocytes and enzyme immunoassays based on peptides with aminoacid sequences which bind the agAAB were used for the antibody diagnostics (both in house assays of E.R.D.E.-AAK-Diagnostik GmbH, Berlin). The action of agAAB on intracellular calcium was studied in primary neonatal rat cardiomyocytes by ratiometric measurements of FURA-2 fluorescence signals. Protein phosphorylation was assessed with Westernblot techniques using phosphorylation site-specific antibodies. The animal experiments were performed with permission