

Prevention of the development of HFpEF by the PDE-5A inhibitor Vardenafil in rats with type 2 diabetes

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Introduction: Heart failure with preserved ejection fraction (HFpEF) shows an increasing prevalence. Specific co-morbidities play a crucial pathophysiological role in the development of HFpEF. Despite its epidemiological relevance, currently available therapies haven't proven to be successful in decreasing the mortality of the disease. The contribution of deteriorated cyclic guanosine monophosphate (cGMP) signalling to the progression of HFpEF has been intensively investigated, while elevated levels of cGMP have been shown to exert cardioprotective effects in cardiovascular diseases. We investigated the effect of long-term preventive application of the phosphodiesterase-5A (PDE-5A) (the enzyme responsible for breaking down cGMP) inhibitor vardenafil in diabetic cardiomyopathy-associated HFpEF.

Methods: Zucker Diabetic Fatty (ZDF) rats were used as a model of HFpEF. ZDFLean rats served as controls. Animals received vehicle (ZDFLean; ZDF) or 10mg/kgBW vardenafil (ZDFLean+Vard; ZDF+Vard) per os from the 7th to 32nd weeks of age. Cardiac function, morphology were assessed by left ventricular (LV) pressure-volume (P-V) analysis and echocardiography at the 32nd week. Key markers of cGMP signalling, nitro-oxidative stress, apoptosis, myocardial hypertrophy and fibrosis were examined.

Results: ZDF animals showed increased LV stiffness (slope of the LV end-diastolic P-V relationship (EDPVR) and prolonged time constant of LV relaxation – markers of diastolic dysfunction –, while systolic performance was preserved. Decreased myocardial cGMP level coupled with impaired protein kinase G (PKG) activity, increased nitro-oxidative stress, enhanced cardiomyocyte apoptosis, hypertrophic and fibrotic remodelling of the myocardium were observed. Vardenafil effectively prevented the development of HFpEF by maintaining diastolic function (decreased LV stiffness and improved LV active relaxation), by restoring cGMP levels and PKG activation, by lowering apoptosis and by alleviating nitro-oxidative stress, myocardial hypertrophy and fibrotic remodelling.

Conclusions: We reported that vardenafil successfully prevented the development of diabetes mellitus associated HFpEF. Thus, PDE-5A inhibition in a preventive manner might be a promising option in the management of HFpEF patients with diabetes mellitus.

Former publications:

Radovits T, Korkmaz S, Mátyás C et al., An altered pattern of myocardial histopathological and molecular changes underlies the different characteristics of type-1 and type-2 diabetic cardiac dysfunction. *J Diabetes Res* 2015; 2015: 728741.

Mátyás C,... Barta BA,... Radovits T. Prevention of the development of heart failure with preserved ejection fraction by the phosphodiesterase-5A inhibitor vardenafil in rats with type 2 diabetes. *Eur J Heart Fail*. 2017; 19: 326-336

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Role of Auto-Antibodies Against the Nicotinic Acetylcholine Receptors in Neurological and Psychiatric Diseases

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Autoimmune diseases affect 6-7% of the world population. In many cases autoantibodies (AA) are involved in these processes. Additionally, in a significant proportion of the general population brain reactive AAs are present in the serum. The potential relation between these AAs and neurological disorders was confirmed in connection with anti-NMDA-receptor encephalitis syndrome, which is an acute form of brain inflammation, potentially lethal, occurring when antibodies produced by the body's own system attack the NMDA receptors in the brain.

According to our hypothesis AAs against nicotinic acetylcholine receptors (nAChRs) have a central role in the development of neuroinflammation and in pathologies affecting brain structures. One example is a major psychiatric disorder, schizophrenia, where 30% of patients do not respond to conventional antipsychotic therapy. In our present research we conducted a comprehensive study of these circulating AAs.

In the first phase of our experiments we tested 165 monoclonal AA samples produced by B-lymphocytes isolated from the liquor of patients with an acute episode of NMDA-R encephalitis syndrome using indirect ELISA method. The antigens used in these experiments were the extracellular domains of the $\alpha 2$, $\alpha 7$ and $\alpha 4\beta 2$ subunits of the nAChR. Of these, 29 were positive in the following distribution: 9 for $\alpha 7$, 8 for $\alpha 4\beta 2$, 1 for $\alpha 2$, 6 for $\alpha 4\beta 2 + \alpha 2$, 1 for $\alpha 4\beta 2 + \alpha 7$, 2 for $\alpha 2 + \alpha 7$, 2 for $\alpha 2 + \alpha 7 + \alpha 4\beta 2$.

In the next phase we tested the functional activity of the samples found positive for $\alpha 7$ in *Xenopus laevis* oocytes expressing $\alpha 7$ -nAChR using voltage clamp technique. In 5 cases the current generated by the activation of these receptors was reduced by more than 50% in the presence of the AAs, suggesting an inhibition of intracellular Ca^{2+} levels.

Based on our results we can conclude that a large number of patients with an acute episode of anti-NMDA-receptor encephalitis syndrome had nAChR-specific and functionally active AA producing cells in their central nervous system. In the next step of our research, we aim to test in vivo the effect of AAs by performing intracerebroventricular osmotic mini-pump infusions in a C57BL/6J animal (mouse) model. This observation opens new perspective in understanding diseases affecting the central nervous system and suggest new therapeutic strategies against autoimmune diseases.

Former publications:

No publications by our laboratory in the topic.

Supervisor(s): Uwe Maskos PhD, senior research fellow, Institut Pasteur, Paris - Department of Neuroscience - Integrative Neurobiology of Cholinergic Systems