

New insights into the diagnostics of autoantibodies against G-protein coupled receptors – pitfalls in the autoantibody detection

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Introduction: The knowledge about the impact of functionally acting autoantibodies which target G-protein coupled receptors (GPCR-AABs) is steadily growing. GPCR-AABs activate receptors; physiological counter-regulation, as known from natural ligands, does, however, not occur. This leads to pathological consequences such as heart failure (here AABs against the beta1-adrenoceptor, beta1-AABs) or other diseases. The problem with the detection of these GPCR-AABs is A) their low titers and B) their functional activity. A) For autoantibodies against the TSH-receptor (Grave's disease) a bioassay (cAMP cascade) revealed titers between 0.0005 and 0.006% of the IgG fraction [Nakatake et al., Thyroid. 2006;16: 1077]. For most of the other GPCR-AABs almost nothing is known about the titer. B) With respect to the functional activity, binding without receptor activation has already been described [Bornholz et al., Cardiovasc Res. 2013;97: 472]. We here tested, if such factors influence on the GPCR-AAB detection.

Methods: A bioassay [Wenzel et al., Heliyon. 2017;3: e00362] and a previously published ELISA [Nagatomo et al., J Am Coll Cardiol. 2017;69: 968] for the detection of the functional activity and the binding of beta1-AABs, respectively, were exploited.

Results: Using the bioassay, beta1-AAB samples were identified and assigned to their epitopes on the receptor using mapping peptides. The samples were also applied onto an ELISA which was specifically developed and previously exploited for a large study investigating "Myocardial Recovery in Patients With Systolic Heart Failure and Autoantibodies Against β 1-Adrenergic Receptors" [Nagatomo et al.]. The comparison revealed that the ELISA results did not match the bioassay outcome.

Conclusion: Since the existence of GPCR-AABs is increasingly gaining clinical importance and plays a decisive role in therapeutic decisions, erroneous measurements can have an enormous impact on patient therapy decisions. That is the reason why reliable tests have to be established which are able to identify the functional active GPCR AABs.