Austin Journal of Pharmacology and Therapeutics

Open Access

Austin Publishing Group

Special Article - Bio Assay

The Unavoidable Need for Bioassays for the Detection of Functionally Active Autoantibodies against G-protein Coupled Receptors

Haberland A*, Hönicke AS, Wallukat G, Göttel P, Müller J and Wenzel K
Berlin Cures GmbH, Berlin, Germany

***Corresponding author:** Haberland A, Berlin Cures GmbH, Berlin, Germany

Received: April 04, 2018; **Accepted:** May 24, 2018; **Published:** May 31, 2018

Short Communication

Knowledge regarding the impact of functionally agonistic autoantibodies targeting G-protein coupled receptors (GPCR-AABs) is steadily growing. These GPCR-AABs activate receptors, however, physiological counter-regulation, as known from natural ligands, does not occur, leading to pathological consequences such as induction and/or maintenance of diseases including heart failure (β1-adrenoceptor) or preeclampsia and systemic sclerosis (AT1- and ETA-receptors, respectively) [1].

The problem with the detection of these autoantibodies is their low titers, making it almost impossible to use solid-phase technology. Interestingly, for autoantibodies against the TSH-receptor, which is involved in Grave's disease, a bioassay using the cAMP cascade revealed quantitation of titers between 0.0005 and 0.006% of the IgG fraction [2].

For autoantibodies targeting the e.g. β2- and α1-adrenoceptor and the AT1, M2, and ETA receptors, no tests based on solid-phase technology have been proven to be able to replace functional assays.

Binding without activation of receptors may be one reason [3], in addition to complete non-specific matrix-binding, as investigated by Güven et al. [4] and Terato et al. [5].

Since β1-AABs occur at a high percentage in heart failure patients, research in this area is most advanced, owing to different therapeutic concepts such as successful immunoadsorption [6-8], attempts to neutralize the autoantibodies via injection of the epitope peptide [9], and most recently the successful neutralization of β1-AABs using an aptamer [10]. The current diagnostic test for the identification of functionally active β1-AABs uses spontaneously beating rat cardiomyocytes [11]; however, a FRET-based assay might possibly also be suitable [12].

Recent endeavors, comparing the bioassay [13] with a solid-phase assay based on native receptor structures (FACS) [14], need to be approached from the perspective of non-specific [4] and non-activating [3] binding, with the use of control cells expressing a different receptor. Thus, despite recent progress in this field, future studies need to be refined.

Conflict of Interest

A. Haberland, AS. Hönicke, G. Wallukat, P. Göttel, J. Müller, and K. Wenzel are employed by Berlin Cures. A. Haberland, G. Wallukat, P. Göttel, and J. Müller are shareholders of the Berlin Cures Holding AG.

References

1. Xia Y, Kellems RE. Receptor-activating autoantibodies and disease: preeclampsia and beyond. Expert Rev Clin Immunol. 2011; 7: 659–674.
2. Nakatake N, Sanders J, Richards T, Burne P, Barrett C, Pra CD, et al. Estimation of serum TSH receptor autoantibody concentration and affinity. Thyroid Off J Am Thyroid Assoc. 2006; 16: 1077–1084.
3. Bornholz B, Weidtkamp-Peters S, Schmitmeier S, Seidel CAM, Herda LR, Felix SB, et al. Impact of human autoantibodies on β1-adrenergic receptor conformation, activity, and internalization. Cardiovasc Res. 2013; 97: 472–480.
4. Güven E, Duus K, Lydolph MC, Jørgensen CS, Laursen I, Houen G. Non-specific binding in solid phase immunoassays for autoantibodies correlates with inflammation markers. J Immunol Methods. 2014; 403: 26–36.
5. Terato K, Do CT, Cutler D, Waritani T, Shionoya H. Preventing intense false positive and negative reactions attributed to the principle of ELISA to re-investigate antibody studies in autoimmune diseases. J Immunol Methods. 2014; 407: 15–25.
6. Müller J, Wallukat G, Dandel M, Bieda H, Brandes K, Spiegelsberger S, et al. Immunoglobulin adsorption in patients with idiopathic dilated cardiomyopathy. Circulation. 2000; 101: 385–391.
7. Wallukat G, Müller J, Hetzer R. Specific removal of beta1-adrenergic autoantibodies from patients with idiopathic dilated cardiomyopathy. N Engl J Med. 2002; 347: 1806.
8. Dandel M, Wallukat G, Potapov E, Hetzer R. Role of β1-adrenoceptor autoantibodies in the pathogenesis of dilated cardiomyopathy. Immunobiology. 2012; 217: 511–520.
9. Nnane IP, Plotnikov AH, Peters G, Johnson M, Kojak C, Vutikullird A, et al. Pharmacokinetics and Safety of Single Intravenous Doses of JNJ-54452840, an Anti-β1-Adrenergic Receptor Antibody Cyclopeptide, in Healthy Male Japanese and Caucasian Participants. Clin Pharmacokinet. 2016; 55: 225–236.
10. Müller J, Haberland A, Becker NP, Wenzel K, Wallukat G, Göttel P, et al. The DNA-Based Therapeutic Agent BC 007 Completely Neutralizes Agonistic Autoantibodies Directed Against β β1-Adrenoceptors: Results of a Phase 1 Trial. JACC 2018; 71: 645.
11. Wenzel K, Schulze-Rothe S, Haberland A, Müller J, Wallukat G, Davideit H. Performance and in-house validation of a bioassay for the determination of beta1-autoantibodies found in patients with cardiomyopathy. Heliyon. 2017; 3: e00362.
12. Nikolaev VO, Boivin V, Störk S, Angermann CE, Ertl G, Lohse MJ, et al. A novel fluorescence method for the rapid detection of functional beta1-adrenergic receptor autoantibodies in heart failure. J Am Coll Cardiol. 2007; 50: 423–431.

Citation: Haberland A, Hönicke AS, Wallukat G, Göttel P, Müller J and Wenzel K. The Unavoidable Need for Bioassays for the Detection of Functionally Active Autoantibodies against G-protein Coupled Receptors. Austin J Pharmacol Ther. 2018; 6(2).1105.

13. Wallukat G, Wollenberger A. Effects of the serum gamma globulin fraction of patients with allergic asthma and dilated cardiomyopathy on chronotropic beta adrenoceptor function in cultured neonatal rat heart myocytes. Biomed Biochim Acta. 1987; 46: S634-639.

14. Bornholz B, Hanzen B, Reinke Y, Felix SB, Jahns R, Schimke I, et al. Detection of DCM-associated β1-adrenergic receptor autoantibodies requires functional readouts or native human β1-receptors as targets. Int J Cardiol. 2016; 202: 728–730.

Austin J Pharmacol Ther - Volume 6 Issue 2 - 2018
ISSN: 2373-6208 | www.austinpublishinggroup.com

Citation: Haberland A, Hönicke AS, Wallukat G, Göttel P, Müller J and Wenzel K. The Unavoidable Need for Bioassays for the Detection of Functionally Active Autoantibodies against G-protein Coupled Receptors. Austin J Pharmacol Ther. 2018; 6(2).1105.