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Detection and functional characterization of angiotensin receptor Type 1 autoantibodies: establishment and clinical translation

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Introduction: Circulating AT1R autoantibodies (AT1R-aabs) directed against the ECL2 of the AT1R with agonist-like activity are supposed to play a pathophysiological role in diseases associated with vascular and renal damage, such as preeclampsia and malignant hypertension (HT), but they are also thought to be involved in heart failure and primary hyperaldosteronism (PHA).
Methods: High-throughput screening assays aiming at a reliable detection of AT1R-aabs in sera from patients with HT and PHA were established. The agonist-like activity of AT1R-aabs was assessed by changes in intracellular calcium levels using Fura2-QBT dye and AlphaLISA SureFire Ultra Assay was used to assess induction of ERK1/2 phosphorylation in stably transfected AT1R-HEK-cells.

Results: IgG purified from sera of n=60 patients with PHA and n=97 with hypertensive heart disease (HT) were screened for their capacity to increase [Ca2+]i or to activate ERK1/2. Ten out of 60 PHA patients increased [Ca2+]i compared to none of the HT-patients, whereas in both disease-entities we detected AT1R-aabs inducing ERK1/2 activation with similar prevalence (PHA: 38%, HT: 31%), indicating the existence of differentially acting AT1R-aabs. PHA-patients positive for ERK1/2 activating AT1R-aabs have lower serum potassium- and renin-levels together with an increased aldosterone concentration concordant with the disease phenotype. Similarly, higher BP values (syst/diast) are observed in AT1R-aab positive HT patients. In addition, ERK1/2-activation induced by either angiotensin II, a mouse AT1R-Mab, or by IgG isolated from patients with PHA or HT could be differentially blocked by the use of various signaling inhibitors. Whereas clinically used AT1R-blockers as e.g. Losartan, Olmesartan, or Candesartan fully block Ang II-mediated ERK activation, they are less efficient in blocking the effects of human AT1R-aabs, with Losartan having almost no effect.

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Conclusion: As hypothesized, the detection of AT1R-aabs directed against the native AT1R based on antigen binding only results in a high number of misleading results. By contrast, functional assays based on AT1R-activation ([Ca2+]i & ERK1/2-phosphorylation) are able to detect AT1R-aabs in 31% or 38% of patients with HT or PHA, respectively.