Letter to the Editor

Adrenergic Cardiovascular Control Before and After Removal of Stimulatory α-1 Adrenoceptor Antibodies

To the Editor:

Agonistic autoantibodies directed against G protein–coupled receptors are implicated in the pathogenesis of various human cardiovascular disorders. A patient subset with idiopathic dilated cardiomyopathy features agonistic antibodies directed against β-1 adrenoreceptors. Subsequently, immunization against β-adrenoreceptors in rats, as well as transfer of serum to nonimmunized animals, induces left ventricular dilation and dysfunction.1 Agonistic antibodies against the angiotensin II subtype 1 receptor may contribute to preeclampsia and humorally mediated kidney transplant rejection. More recent studies identified agonistic antibodies against the angiotensin II subtype 1 receptor produced mesentery artery segment contraction.2 Finally, 5 patients in whom agonistic α-1 adrenoreceptor antibodies were removed through immunoadsorption showed favorable blood pressure responses.2 Another study arrived at similar conclusions after infused antibodies rapidly raised blood pressure in anesthetized rats; prazosin abolished the response.3 However, how agonistic α-1 adrenoreceptor antibodies might affect cardiovascular adrenergic regulation in humans is unknown. To address this issue, we tested responses to physiological sympathetic nervous system stimuli and exogenous adrenergic agonists before and after immunoadsorption.

We studied 5 patients (4 men and 1 woman; 58 ± 4 years; 31 ± 2 kg/m²) with treatment-resistant arterial hypertension and agonistic α-1 adrenoreceptor antibodies whose office blood pressure data have been included in a previous report.2 Patients received no antihypertensive medications. All of the other antihypertensive medications were kept constant throughout the study. Patients underwent immune adsorption on 5 consecutive days. At each session, the calculated plasma volume was passed through adsorption columns at 50 mL/min. Levels of antibodies against the α₁-adrenergic receptor were measured by a bioassay using spontaneously beating rat cardiomyocytes. Immune adsorption substantially reduced α₁-adrenoreceptor autoantibodies (24 ± 1 Δhpm/min before versus 5 ± 1 Δhpm/min after immune adsorption; P < 0.001). Before and 5 to 12 days after immune adsorption, we conducted a battery of autonomic function tests and sensitivity testing with incremental intravenous phenylephrine and nitroprusside doses. ECG and beat-by-beat finger blood pressure (Finapres) were continuously recorded. Brachial blood pressure was monitored to assess absolute blood pressure levels (Dinamap). The local ethics committee approved the study, and written-informed consent was obtained. All data are expressed as mean ± SEM.

Before immune adsorption, supine blood pressure was 169 ± 12/88 ± 7 mm Hg, 58 ± 6 bpm. After completion of the immune adsorption protocol, blood pressure was reduced in 4 patients and increased in 1 patient (group average: 146 ± 11/78 ± 3 mm Hg; P = 0.095/0.238). Resting heart rate was 59 ± 5 bpm before immune adsorption and 59 ± 4 bpm after immune adsorption. Before and after immune adsorption, blood pressure and heart rate responded normally to graded head-up tilt testing. Chronic vascular adrenoreceptor stimulation should decrease adrenergic responsiveness through receptor occupancy and/or desensitization. Yet, with handgrip testing, systolic blood pressure increased 33 ± 10 mm Hg before and 37 ± 4 mm Hg after immune adsorption (not significant). With cold pressor testing, systolic blood pressure increased 18 ± 9 mm Hg before and 14 ± 4 mm Hg after immune adsorption (not significant). Nitroprusside elicits baroreflex-mediated vascular α-adrenoreceptor activation restraining the hypotension.4 The depressor response to nitroprusside was identical before and after immune adsorption (Figure). Finally, the pressor response to direct α-adrenoreceptor stimulation with phenylephrine was within a normal range and unaffected by immune adsorption (Figure). Phenylephrine and nitroprusside-induced heart rate responses were identical in 4 patients and increased in 1 patient (group average: 146 ± 11/78 ± 3 mm Hg; P = 0.095/0.238). Resting heart rate was 59 ± 5 bpm before immune adsorption and 59 ± 4 bpm after immune adsorption. Before and after immune adsorption, blood pressure and heart rate responded normally to graded head-up tilt testing. Chronic vascular adrenoreceptor stimulation should decrease adrenergic responsiveness through receptor occupancy and/or desensitization. Yet, with handgrip testing, systolic blood pressure increased 33 ± 10 mm Hg before and 37 ± 4 mm Hg after immune adsorption (not significant). With cold pressor testing, systolic blood pressure increased 18 ± 9 mm Hg before and 14 ± 4 mm Hg after immune adsorption (not significant). Nitroprusside elicits baroreflex-mediated vascular α-adrenoreceptor activation restraining the hypotension.4 The depressor response to nitroprusside was identical before and after immune adsorption (Figure). Finally, the pressor response to direct α-adrenoreceptor stimulation with phenylephrine was within a normal range and unaffected by immune adsorption (Figure). Phenylephrine and nitroprusside-induced heart rate responses were identical before and after immune adsorption.
before and after immune absorption. The observation excludes the possibility that altered vascular responses were masked by opposing changes in baroreflex heart rate regulation.

Antibody removal through immune absorption or plasma exchanges is an excellent approach to test the physiological relevance of antibodies directed against autonomic nervous system structures. For example, removal of inhibitory antibodies against ganglionic nicotinic acetylcholine receptors acutely improved autonomic dysfunction. Yet, in the present study, patients with treatment-resistant hypertension and autoantibodies against α-1 adrenergoreceptors showed normal acute cardiovascular responses to physiological and pharmacological adrenergic stimuli. Antibody removal did not alter the response. Our observations challenge the idea that endogenous α-1 adrenergoreceptor antibodies act like small molecule adrenergic agonists in vivo. Our study does not exclude that agonistic α-1 adrenergic receptor antibodies chronically affect cardiovascular structure and function in patients with resistant hypertension. However, we strongly suggest that experimental findings cannot be simply extrapolated to patients with endogenously produced antibodies and that controlled clinical trials are required.

Disclosures

None.

References


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Hypertension. 2012;59:e6-e7; originally published online December 27, 2011;
doi: 10.1161/HYPERTENSIONAHA.111.188177

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