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Renal Ischemia and Transplantation Predispose to Vascular Constriction Mediated by Angiotensin II Type 1 Receptor-Activating Antibodies.

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Source

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Abstract

BACKGROUND:

We previously described angiotensin II type 1 receptor-activating antibodies (AT1R-Abs) in renal transplant recipients with vascular rejection and malignant hypertension. In this study, we tested the hypothesis that AT1R-Abs can cause renal artery contraction by AT1R activation with renal ischemia representing a key permissive factor and therefore contribute to renal pathologic condition.

METHODS:

Isolated renal and mesenteric arteries from Lewis rats were incubated with purified AT1R-Abs from patients with human leukocyte antigen antibody-negative vascular rejection. Vascular contraction was measured using small vessel myography. The measurements were repeated with renal arteries derived from native kidneys subjected to ischemia-reperfusion or after transplantation in a low-responder Fischer 344-to-Lewis rat kidney-transplantation model.

RESULTS:

AT1R-Abs acted in a vascular bed-specific manner and caused small contractions only in native rat renal arteries but not in mesenteric arteries. AT1R-Abs did not alter the vascular reactivity to phenylephrine, angiotensin II, or acetylcholine in native renal arteries. In contrast, AT1R-Abs caused a pronounced (>10-fold) contraction of renal arteries after ischemia and after allogeneic transplantation. Pretreatment with pharmacologic AT1R blocker only partially inhibited the AT1R-Abs-induced contraction, which was almost completely abolished by neutralizing peptides targeting epitopes of AT1R-Abs on the second loop of AT1R.

CONCLUSIONS:

These data demonstrate that AT1R-Abs can induce renal vascular contraction under predisposing conditions such as in ischemic or transplanted kidneys. Neutralizing antibodies against specific epitopes in the AT1R can ameliorate this contraction.