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Tamsulosin attenuates abdominal aortic aneurysm growth ☆,☆☆

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ABSTRACT

Background: Tamsulosin, an α_{1A}-adrenergic receptor inhibitor, is prescribed to treat benign prostatic hyperplasia in men >60 years of age, the same demographic most susceptible to abdominal aortic aneurysm. The goal of this study was to investigate the effect of tamsulosin on abdominal aortic aneurysm pathogenesis.

Methods: Abdominal aortic aneurysms were induced in WT C57BL/6 male mice ($n = 9$-18/group), using an established topical elastase abdominal aortic aneurysm model. Osmotic pumps were implanted in mice 5 days before operation to create the model, administering either low dose (0.125 μg/day tamsulosin), high dose (0.250μg/day tamsulosin), or vehicle treatments with and without topical application of elastase. Blood pressures were measured preoperatively and on postoperative days 0, 3, 7, and 14. On postoperative day 14, aortic diameter was measured before harvest. Sample aortas were prepared for histology and cytokine analysis.

Results: Measurements of systolic blood pressure did not differ between groups. Mice treated with the low dose of tamsulosin and with the high dose of tamsulosin showed decreased aortic diameter compared with vehicle-treated control (93% ± 24 versus 94% ± 30 versus 132% ± 24, respectively; $P = .0003$, $P = .0003$). Cytokine analysis demonstrated downregulation of pro-inflammatory cytokines in both treatment groups compared with the control ($P < .05$). Histology exhibited preservation of elastin in both low- and high-dose tamsulosin-treated groups ($P = .0041$ and $P = .0018$, respectively).

Conclusion: Tamsulosin attenuates abdominal aortic aneurysm formation with increased preservation of elastin and decreased production of pro-inflammatory cytokines. Further studies are necessary to elucidate the mechanism by which tamsulosin attenuates abdominal aortic aneurysm pathogenesis.

Introduction

Abdominal aortic aneurysms (AAAs) were the primary cause of 9,863 deaths in 2014, making this disease the 10th leading cause of death for men >65 years of age in the United States.[1,2] The risk of AAA rupture is associated with size and rate of expansion.[3] AAA rupture is associated with a mortality of 50%–80%, and operative repair carries substantial morbidity.[4] Currently, there is no medical therapy for AAA, and operative repair represents the only intervention to treat this disease.

The α_{1A}-adrenergic receptor, a G protein-coupled receptor (GPCR), is located in the prostate but also on the membrane of vascular smooth muscle cells (VSMCs), which comprise a substantial portion of the aortic wall and play an important role in the pathogenesis of AAAs.[5,6] Activation of this GPCR ultimately leads to stimulation of muscle contraction via the inositol trisphosphate (IP3) and diacylglycerol (DAG) pathway. The receptor first sends phospholipase C to cleave phosphatidylinositol bisphosphate (PIP2), a membrane phospholipid, into IP3 and DAG. DAG remains in the membrane and later activates protein kinase C (PKC).[7] IP3, a phosphorylated second messenger suggested to be involved in AAA pathogenesis, travels into the cell, binds to L-type calcium channels, and leads to release of intracellular Ca^{2+} from both the endoplasmic reticulum and store-operated Ca^{2+} channels further down

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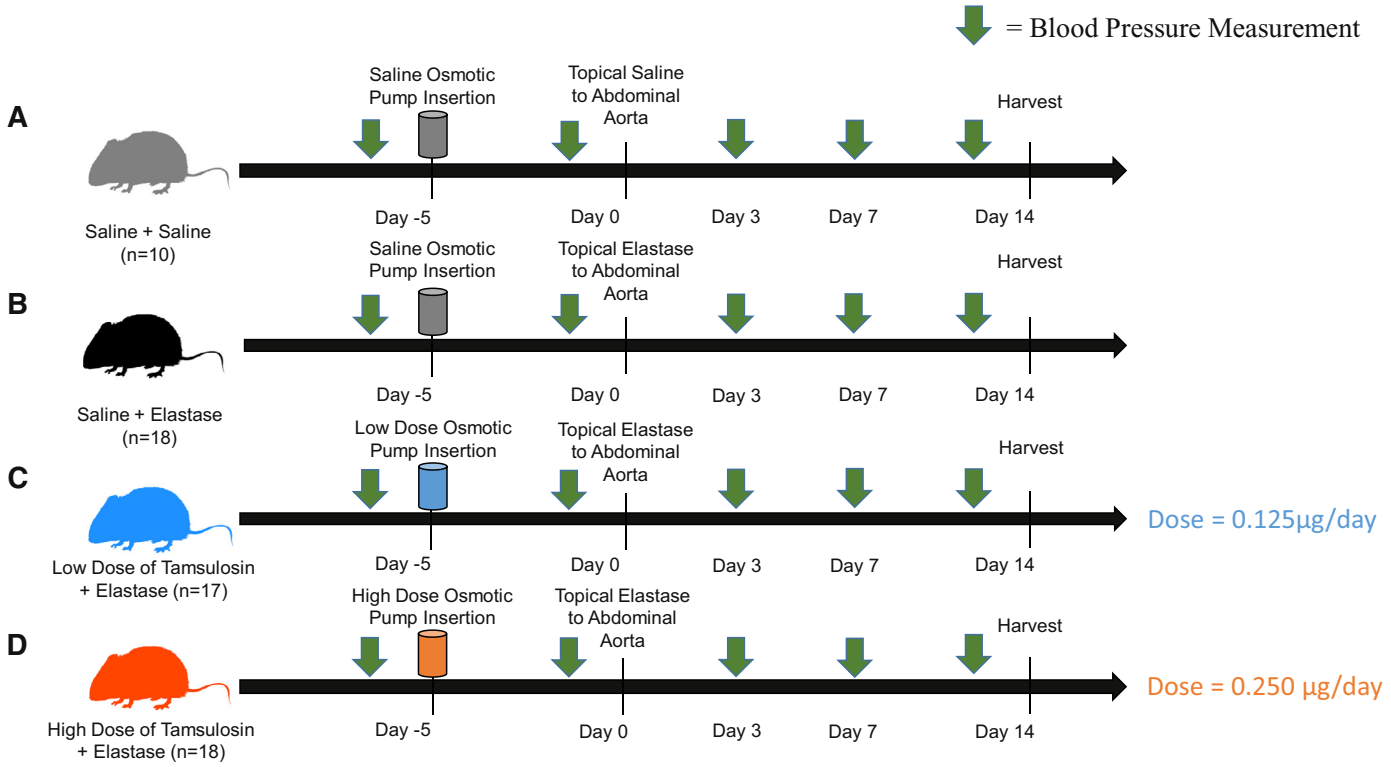

Fig. 1. Blood pressure measurement, topical elastase and tamsulosin treatment experiment design. (*A*) Saline + Saline group: Blood pressure measurements were taken on day –5, 0, 3, 7, and 14 for all groups. Osmotic pumps containing sterile saline were implanted in the mice and sterile saline was applied topically to the aorta. Tissue was harvested on day 14. (*B*) Saline + Elastase group: Osmotic pumps containing sterile saline were implanted in the mice and elastase was used to induce AAA. (*C*) Low Dose + Elastase group: Osmotic pumps administering 0.125 µg/day of tamsulosin HCl were implanted in the mice and elastase was used to induce AAA. (*D*) High Dose + Elastase group: Osmotic pumps administering 0.250 µg/day of tamsulosin HCl were implanted the mice and elastase was used to induce AAA. There was no difference between any group at any time point ($P > .05$).

the pathway.[7–8] Activation of this pathway results in increased intracellular free Ca^{2+} concentration and ultimately, vascular smooth muscle contraction.

Tamsulosin is an α_{1A}-adrenergic receptor inhibitor commonly prescribed to treat benign prostatic hyperplasia (BPH) in men >60years old, the same demographic most susceptible to AAA formation. Histologic evidence of BPH has been observed at 8% of men in their thirties and increases to more than 70% prevalence in men >60 years of age.[9] The demand for BPH treatment, such as tamsulosin, will likely increase in the United States as the population ages.[10] By inhibiting the α_{1A}-adrenergic receptor, tamsulosin decreases the amount of IP3 in VSMCs and the downstream products that result from this pathway. The goal of this study was to investigate the effect of tamsulosin, an FDA-approved drug for the treatment of BPH, on AAA pathogenesis, because it was hypothesized that it would attenuate AAA size and rate of growth in a manner independent of blood pressure.

Methods

Animal housing

We placed 8- to 12-week old WT C57BL/6 male mice (Jackson Laboratory, Bar Harbor, ME) in housing that was maintained at 70°F and 50% humidity in 12-hour light-dark cycles as required by our institutional animal protocols. All mice were provided drinking water and fed either a minimal phytoestrogen diet (2017 Teklad Global 16% Protein Rodent Diet, Harlan Labs, Inc., Frederick, MD). Animal protocols were approved by the Institutional Animal Care and Use Committee (No. 3848) of the University of Virginia, Charlottesville.

Blood pressure measurement

In a previously described procedure, blood pressure measurements were taken using a non-invasive, tail-cuff system under basal conditions.[11] In short, blood pressure was measured using the MC4000 Multi Channel Blood Pressure Analysis System (Hatteras Instruments, Cary, NC) in representative mice from each group ($n = 4$/group) per the manufacturer recommendations. The mice were restrained and blood pressures measured 5 days preoperatively, on the day of AAA induction surgery, and on postoperative days 3, 7, and 14. For each mouse, 10 sets of systolic and diastolic measurements were taken and averaged to estimate more accurately their blood pressures during the session. Systolic blood pressure was used when comparing the groups.

Drug administration

On preoperative day 5, osmotic infusion pumps (Alzet 1004, Durect Corp, Cupertino, CA) continuously administering either sterile saline ([0.9% NaCL] $n = 10$, Fig. 1, *A*; $n = 18$, Fig. 1, *B*), a low dose of 0.125µg/day of tamsulosin hydrochloride (HCl; Sigma-Aldrich, St. Louis, MO) ($n = 17$, Fig. 1, *C*), or a high dose of 0.250 µg/day of tamsulosin HCl ($n = 18$, Fig. 1, *D*) were implanted subcutaneously into 8- to 12-week old C57BL/6 mice, using previously described methods.[12–15] Tamsulosin treatment started 5 days before the operation to allow the drug to reach a steady state before AAA induction.[16] Dosages administered to mice (25g) in the experiment are proportional by weight to the dosages prescribed clinically (0.4mg/day and 0.8mg/day) to the average human (75kg).

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