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| Educational Level * | PhD Candidate |
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| College * | College of Medicine |
| Department * | Department of Pharmacology |
| Title of Research * | A Small Molecule Inhibitor of Signal Transducer and Activator of Transcription 3 (STAT3) Protects Against Angiotensin II-Induced Vascular Dysfunction and Hypertension |
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| Introduction & Purpose * | Signal transducer and activator of transcription 3 (STAT3) is a transcription factor known to play key roles in development, cytokine signaling, and cellular growth. Angiotensin II (Ang II) promotes oxidative stress and inflammation, both of which contribute to vascular disease. Ang II promotes inflammation in part by formation of proinflammatory cytokines that lead to activation of STAT3. We tested if STAT3 is essential for Ang II-induced vascular dysfunction and hypertension. |
| Experimental Design * | Responses of carotid arteries from C57BL6 mice were examined in vitro after 22-hour incubation with vehicle or Ang II (10 nM) in the presence or absence of an inhibitor of STAT3 activation, S3I-201. Blood pressure (BP) was examined from C57BL6 mice infused with either saline or Ang II (1.4 mg/kg/day) for 14 days via osmotic minipump, with or without S3I-201 treatment, a STAT3 inhibitor (5 mg/kg IP, q.o.d.) (n=5). |
| Results * | Ang II incubation increased vascular superoxide (~2 fold) and reduced the endothelium-dependent agonist acetylcholine (Ach) responses by ~50% vs. controls ($P < 0.05$), which were prevented by co-incubation with S3I-201 (10 μ M). Similar findings were obtained with Stattic, a second small molecule inhibitor of STAT3 activation. Ang II increased BP (tail cuff plethysmography) compared to control animals (155 ± 2 and 112 ± 2 mmHg, respectively; $P < 0.001$). S3I-201 reduced BP slightly in control (102 ± 2) and blocked Ang II-induced increases (114 ± 3). Ach produced relaxation in control carotid arteries studied in vitro ($101 \pm 1\%$), which response was significantly impaired by Ang II ($72 \pm 3\%$, $P < 0.05$). S3I-201 treatment attenuated the relaxation effects of Ang II ($94 \pm 4\%$) with no effect in controls ($101 \pm 1\%$). In basilar artery, a cerebral resistance artery, Ang II impaired Ach responses by ~ 50% that were protected by S3I-201. |
| Conclusions * | In summary, these findings provide the first evidence that STAT3 plays an essential role in Ang II-induced vascular dysfunction. These findings also provide novel evidence that targeting STAT3 with small molecule inhibitors, or other future approaches, may have beneficial effects during hypertension. |

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