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College *	College of Medicine
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Title of Research *	Small Molecule Inhibitors of Signal Transducer and Activator of Transcription 3 Protect from Angiotensin II-induced Vascular Dysfunction
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Introduction & Purpose *	Signal transducer and activator of transcription 3 (STAT3) is a transcription factor activated by tyrosine kinases 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. We tested the hypothesis that STAT3 plays a role in Ang II-induced vascular dysfunction.
Experimental Design *	Responses of carotid arteries from C57BL6 mice to the endothelium dependent dilator acetylcholine 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. Ang II induced increases in vascular superoxide was measured by lucigenin enhanced chemiluminescence.
Results *	The endothelium-dependent agonist acetylcholine (Ach) produced relaxation in arteries treated with vehicle and the response was inhibited by ~50% by Ang II (P<0.01). Ang II increased vascular superoxide more than 2-fold (P<0.05) measured with chemiluminescence. S3I-201 (10 µM) prevented effects of Ang II on superoxide and responses to Ach. Relaxation to nitroprusside was not altered in any group. In contrast to these findings, lipopolysaccharide (0.5 µg/ml) induced endothelial dysfunction was not altered by S3I-201. Similar findings were obtained with Stattic, a second small molecule inhibitor of STAT3 activation.
Conclusions *	These findings provide the first evidence that STAT3 plays an essential role in Ang II-induced vascular dysfunction.

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