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# Chronic overexpression of angiotensin-(1-7) in rats reduces cardiac reactivity to acute stress and dampens anxious behavior

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## Abstract

Angiotensin II (Ang II) acts as a pro-stress hormone, while other evidence indicates that angiotensin-(1-7) [Ang-(1-7)] attenuates physiological responses to emotional stress. To further test this hypothesis, in groups of 5–6 rats we evaluated autonomic, cardiovascular and behavioral parameters in male Sprague-Dawley (SD) and transgenic TGR(A1-7)3292 (TG) rats chronically overexpressing Ang-(1-7). Compared to SD rats, TG rats showed reduced baseline heart rate (HR; SD  $380 \pm 16$  versus TG  $329 \pm 9$  beats per minute (bpm), mean  $\pm$  standard error of mean,  $p < .05$ ) and renal sympathetic discharge (SD  $138 \pm 4$  versus TG  $117 \pm 5$  spikes/second,  $p < .05$ ). TG rats had an attenuated tachycardic response to acute air-puff stress ( $\Delta$ HR: SD  $51 \pm 20$  versus TG  $1 \pm 3$  bpm;  $p < .05$ ), which was reversed by intracerebroventricular injection of the Mas receptor antagonist, A-779 ( $\Delta$ HR: SD  $51 \pm 20$  versus TG  $63 \pm 15$  bpm). TG rats showed less anxious behavior on the elevated plus maze, as revealed by more entries into open arms (SD  $2 \pm 2$  versus TG  $47 \pm 5\%$  relative to total entries;  $p < .05$ ), and more time spent in the open arms (SD  $5 \pm 4$  versus TG  $53 \pm 9\%$  relative to total time,  $p < .05$ ). By contrast with SD rats, diazepam (1.5 mg/kg, intraperitoneally) did not further reduce anxious behavior in TG rats, indicating a ceiling anxiolytic effect of Ang-(1-7) overexpression. Ang-(1-7) concentrations in hypothalamus and plasma, measured by mass spectrometry were two- and three-fold greater, respectively, in TG rats than in SD rats. Hence, increased endogenous Ang-(1-7) levels in TG rats diminishes renal sympathetic outflow and attenuates cardiac reactivity to emotional stress, which may be via central Mas receptors, and reduces anxious behavior.

**Lay summary** We used a genetically modified rat model that produces above normal amounts of a peptide hormone called angiotensin-(1-7) to test whether this peptide can reduce some of the effects of stress. We found

that angiotensin-(1-7), acting in the brain, can reduce anxiety and reduce the increase in heart rate associated with emotional stress. These findings may provide a lead for design of new drugs to reduce stress.

Keywords: [Angiotensin-\(1-7\)](#), [anxiety](#), [emotional stressor](#), [heart rate](#), [renal sympathetic activity](#), [transgenic](#)

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## Additional information

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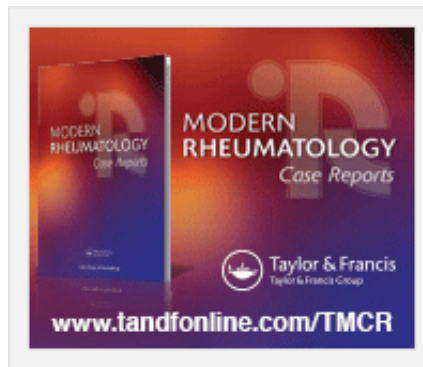
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