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

Danielle Moura Santos, Fernanda Ribeiro Marins, Marcelo Limborço-Filho, Marilene Luzia de Oliveira, Daniele Hamamoto, Carlos Henrique Xavier, Fabrício Araújo Moreira, Robson Augusto Souza Santos, Maria José Campagnole-Santos & Marco Antonio Peliky Fontes

Pages 189-196 | Received 01 Apr 2016, Accepted 15 Feb 2017, Published online: 13 Mar 2017

Download citation  http://dx.doi.org/10.1080/10253890.2017.1296949
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 ± 16 versus TG 329 ± 9 beats per minute (bpm), mean ± standard error of mean, p < .05) and renal sympathetic discharge (SD 138 ± 4 versus TG 117 ± 5 spikes/second, p < .05). TG rats had an attenuated tachycardic response to acute air-puff stress (ΔHR: SD 51 ± 20 versus TG 1 ± 3 bpm; p < .05), which was reversed by intracerebroventricular injection of the Mas receptor antagonist, A-779 (ΔHR: SD 51 ± 20 versus TG 63 ± 15 bpm). TG rats showed less anxious behavior on the elevated plus maze, as revealed by more entries into open arms (SD 2 ± 2 versus TG 47 ± 5% relative to total entries; p < .05), and more time spent in the open arms (SD 5 ± 4 versus TG 53 ± 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

Additional information

Funding

We express thanks for financial support from Brazilian agencies: CNPq (PQ30600/2013-0), Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG), PRONEX, INCT-Nanobiofar (CNPq/Fapemig), CAPES, and from the German agency DFG, and from Labfar (Alamantec) who performed the mass spectrometry analysis.
Chronic overexpression of angiotensin-(1-7) in rats reduces cardiac reactivity to acute stress and dampens anxious behavior: Stress: Vol 20, No 2
Review

Therapeutic uses for Angiotensin-(1-7) ➜

Alice Machado-Silva et al.
Expert Opinion on Therapeutic Patents

Published online: 2 May 2016
Chronic overexpression of angiotensin-(1-7) in rats reduces cardiac reactivity to acute stress and dampens anxious behavior: Stress: Vol 20, No 2

Chronic overexpression of angiotensin-(1-7) in rats reduces cardiac reactivity to acute stress and dampens anxious behavior: Stress: Vol 20, No 2