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Brain angiotensin-(1–7)/Mas axis: A new target to reduce the cardiovascular risk to emotional stress

Marco Antônio Peliky Fontes [a,*], Augusto Martins Lima [c], Robson Augusto Souza dos Santos [a,b,*]

[a] National Institute of Science and Technology in Nanobiopharmaceutics (INCT — Nanobiofar), Department of Physiology and Biophysics, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil
[b] Institute of Cardiology, University Foundation of Cardiology, Porto Alegre, Rio Grande do Sul, Brazil
[c] Institute of Physiological Chemistry and Pathobiochemistry, University of Münster, Münster, Germany

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ABSTRACT

Emotional stress is now considered a risk factor for several diseases including cardiac arrhythmias and hypertension. It is well known that the activation of neuroendocrine and autonomic mechanisms features the response to emotional stress. However, its link to cardiovascular diseases and the regulatory mechanisms involved remain to be further comprehended. The renin–angiotensin system (RAS) plays an important role in homeostasis on all body systems. Specifically in the brain, the RAS regulates a number of physiological aspects. Recent data indicate that the activation of angiotensin-converting enzyme/angiotensin II/AT_1 receptor axis facilitates the emotional stress responses. On the other hand, growing evidence indicates that its counterregulatory axis, the angiotensin-converting enzyme 2 (ACE2)/(Ang)iotensin-(1–7)/Mas axis, reduces anxiety and attenuates the physiological responses to emotional stress. The present review focuses on angiotensin-(1–7)/Mas axis as a promising target to attenuate the physiological response to emotional stress reducing the risk of cardiovascular diseases.

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1. Introduction

Psychological or emotional stress can be defined as a subjective perception of a potential or real environmental threat or challenge. This condition leads to physiological changes that, in nature, improve animal reaction and chances of survival facing environmental threats. Unfortunately, however, anxiety, anger, hostility and frustration are included in the costs of the urbanized and competitive modern life. Indeed, it is now well recognized that chronic exposure to negatively charged mental events can cause several diseases (Golbidi et al., 2015). Currently, emotional stress is considered a potential modifiable risk factor for cardiovascular disease (Steptoe and Kivimaki, 2012) including, cardiac arrhythmias (Taggart et al., 2011), hypertension (Esler et al., 2008) and sudden cardiac death (Lampert, 2009). The psychosocial factors involved are numerous, including, depression, anxiety, personality factors and character traits, social isolation and chronic and subacute life stress (Rozanski et al., 1999). It is important to consider that the individual vulnerability or hyperresponsiveness to stressors likely involves particular early life experiences and/or genetic background.

* Corresponding authors at: Laboratório de Hipertensão. Departamento de Fisiologia e Biofísica, ICB, Universidade Federal de Minas Gerais, Belo Horizonte, MG 31270 901, Brazil.
E-mail addresses: peliky@icb.ufmg.br (M.A.P. Fontes), robsonsant@gmail.com (R.A.S. Santos).

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Emotional stress activates the neurohumoral hypothalamo-pituitary adrenocortical (HPA) outflow, represented mainly by elevated adrenocorticotropic hormone (ACTH) levels, and changes autonomic outflow (sympathetic and parasympathetic) to different target organs (Pacak and Palkovits, 2001; Fontes et al., 2014) (Fig. 1). In the short term, mental stress in humans causes significant increases in sympathetic activity, heart rate and blood pressure (Callister et al., 1992; Carter et al., 2005). The sympathetic response pattern during mental stress preferentially involves the heart, as demonstrated by regional plasma norepinephrine spillover (Esler et al., 1989). The arterial pressure response accompanies the intensity of stress challenge and is primarily influenced by the intensity of the tachycardic response (Callister et al., 1992).

Although there has been substantial progress in understanding the central pathways involved in the cardiovascular response to emotional stress (Fontes et al., 2011), several additional regulatory mechanisms influencing these pathways during the stress response remain poorly understood. In this regard, the involvement of renin–angiotensin system (RAS) peptides deserves particular attention. Recent literature subdivides the RAS into two distinct axes, the angiotensin-converting enzyme/angiotensin II/AT_1 receptor axis and its counterregulatory axis, the angiotensin-converting enzyme 2 (ACE2)/(Ang)iotensin-(1–7)/Mas axis (Fraga-Silva et al., 2013). Apart from its peripheral actions, findings from several previous studies indicate that peptides of the RAS may act in the brain regulating a number of physiological processes (Grobe et al., 2008). The effects of angiotensin (Ang) peptides during stress responses likely result from an integration of actions by circulating peptides and brain peptides derived from neuronal and glial sources (Arnold et al., 2012). Since the role of Ang II as a major pro-stress hormone has been elegantly revised before (Saavedra and Benicky, 2007), only the most relevant aspects are mentioned. The present review discusses the possibility that the activation of ACE2/Ang-(1–7)/Mas axis may reduce the risk of stress-related diseases attenuating the harmful effect produced by overactivation of physiological response to emotional stress. We will cover the role of Ang-(1–7)/Mas axis on behavioral, cardiovascular and other functional aspects influenced by emotional stress.

2. The renin angiotensin system

The formation of the biologically active end-product of this peptidic hormonal system occurs by a limited proteolysis process starting with the precursor, the glycoprotein angiotensinogen by renin (Fig. 2). This step occurs in the circulation but also in many organs and tissues (Bader et al., 2012). Angiotensin I is the product of the angiotensinogen hydrolysis by renin. The formation of the octapeptide Ang II from Ang I is mainly dependent of angiotensin-converting enzyme (ACE), a dipeptidyl carboxyl-peptidase. Ang II is widely expressed, including the endothelium, a strategic localization for the formation of circulating Ang II. The lung vascular territory plays a pivotal role in this process. In addition to Ang II, other biologically active end-products are formed in the RAS including Ang III, Ang IV and Ang-(1–7). Furthermore, other two peptides, Ang A and alamandine can be formed by replacement of asparagine by alanine, a process involving decarboxylation of the aspartate residue. Alamandine formation can also occur by hydrolysis of Ang A by ACE2 (Bader et al., 2012; Passos-Silva et al., 2015). Ang III and IV formation is dependent of aminopeptidases while the formation of

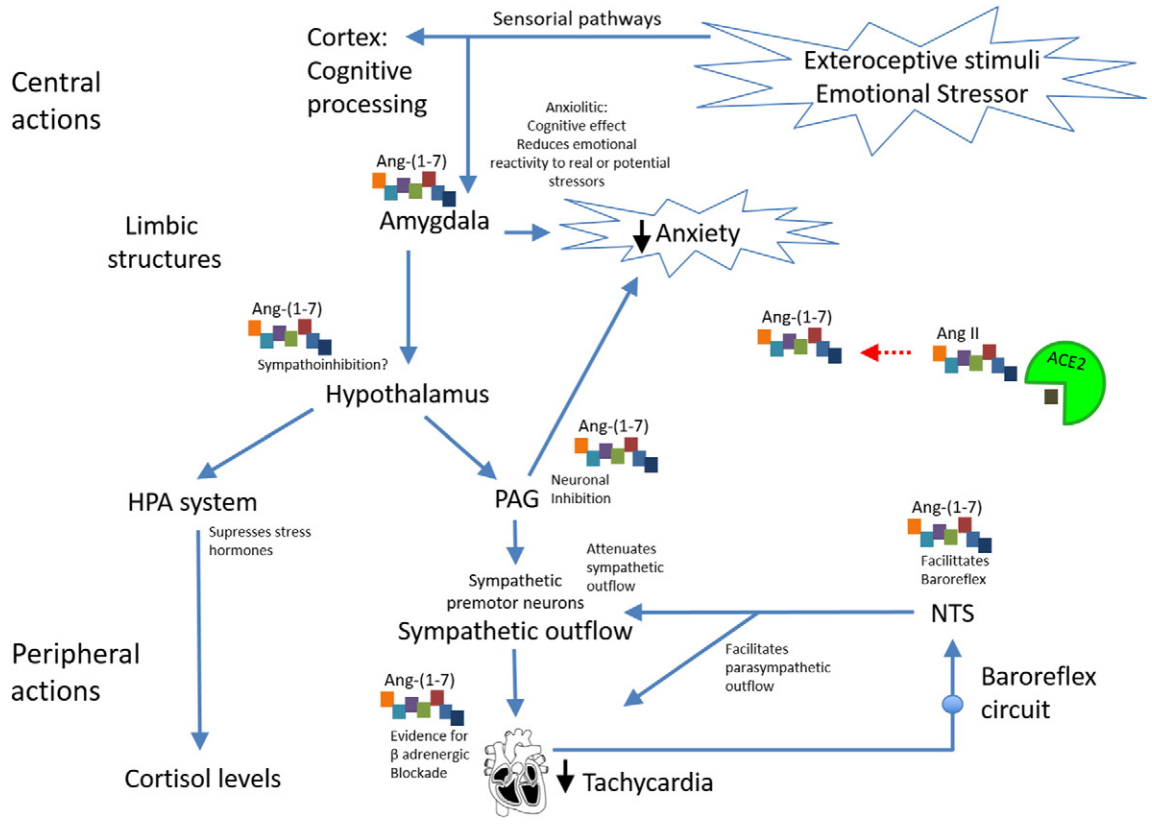

Fig. 1. Schematic diagram based on functional and anatomic studies showing central and peripheral mechanisms by which angiotensin-(1–7) could act to attenuate the effects of emotional stress. Stressful stimuli are processed via sensorial pathways and activate brain regions that subserve emotion influencing cognition, anxiety, endocrine and autonomic responses. Centrally, Ang-(1–7), formed via ACE2, could reduce anxiety acting in the amygdala and periaqueductal gray (PAG). Reduction of anxiety leads to reduction in sympathetic outflow. Direct inhibitory actions in the hypothalamus and PAG could also reduce sympathetic outflow to target organs. Facilitation of baroreflex-induced bradycardia could offer cardiovascular protection during stress responses. Peripherally, Ang-(1–7) interference with β1-adrenergic receptors could block the direct sympathetic input to the heart reducing the cardiac risk to stress such as arrhythmogenesis. Suppression of HPA axis and stress hormones could minimize the long term effects of chronic stress such as gastric ulcerations. Possibilities are given according to the review discussion (see text for details).