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Table of Contents

GLOBAL HEALTH LAW JOURNAL - Volume 1 - nº 02- 2023

STRESS RESPONSE AS A PROMINENT CARDIOVASCULAR RISK FACTOR [1]

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Stress response as a prominent cardiovascular risk factor

Abstract

According to health organizations, at least one third of the diseases that lead people to seek medical care are related to stress. The current conditions of life in the world represent the major source of stress in humans, the so-called psychosocial stress, caused by the accelerated process of urbanization and unhealthy lifestyles. Stress is defined as the organism response to any potential or real challenge or threat to its physical or emotional integrity. Stress response is an arrangement of adaptive mechanisms essential to guarantee survival, whereby a protective mechanism by preparing the organism to defend, to flee or to adapt to the stressful situation. However, over a threshold, it can be harmful, leading to higher susceptibility to disease. The turning point of stress from a beneficial reaction to a risk factor for diseases, is still unknown. In this review, we assess multiple studies about stress concept, molecular mechanisms of stress response and it physiological implications to support the association of stress as a disease risk factor, particularly as a cardiovascular risk factor.
Keywords: stress, psychological stress, physiological stress response, cardiovascular risk factor, molecular mechanism.

Introduction

Life is accompanied by constant challenges and threats that activate survival mechanisms. Such mechanisms are highly conservative and contribute to the organisms' formidable resilience (FUCHS & STELLER, 2015; GALLUZZI et al., 2018). When genetically programmed expectations, which are

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established by previous learning or by the circumstances, do not correspond to the actual or potential perceptions of the external and internal environments, those mechanisms are triggered and constitute the stress reaction (McEWEN, 2000; KOOLHAAS et al., 2011). Therefore, the main objective of the stress reaction is to ensure survival in face of adverse situations, but when the reaction is too intense, prolonged or repeated, or even when it causes frustration, stress can trigger deep physiological changes that start disruptive processes (McEWEN, 2000; CARRASCO & VAN DE KAR, 2003; DE CARVALHO et al., 2021). The turning point of stress from a beneficial reaction to a risk factor for various diseases, is still unknown, although it is now accepted that at least one third of the diseases that lead people to seek medical care are related to stress.

The current conditions of life in the world represent a major cause of stress in humans, the so-called psychosocial stress, caused by the accelerated process of urbanization and unhealthy lifestyles. In this review, we will focus on the concept of stress and on its effects, which have been reported in more than 30 years of research in the Laboratory of Stress Biology (BEST). More specifically, the environmental stress induced alterations in the adrenergic signaling in the heart and the consequences of those alterations to cardiac performance.

Stress concept

The concept of stress was developed from the innovative contributions of Claude Bernard (HOLMES, 1986), Walter Cannon (1935), and Hans Selye (1936). Stress was defined as the organism response to any potential or real challenge or threat to its physical or emotional integrity. The stress reaction aims to guarantee survival during adversity by mobilizing resources to support the Cannon's "fight or flight reaction", while preserving homeostasis (McEWEN, 2007; SPADARI-BRATFISCH & DOS SANTOS, 2008).

It has been proposed that the stress reaction is accomplished by the "stress system" with central and peripheral components (CHARMANDARI et al., 2005). The central components include the hypothalamic paraventricular nuclei, that release the corticotropin releasing factor (CRF) and arginine-vasopressin (AVP), as well as the CRF neurons in the Parabrachial nucleus and noradrenergic neurons in the Locus Coeruleus. The peripheral components are the Sympathetic Nervous System – Adrenal Medulla (SNSAM) and the Hypothalamus—Pituitary-Adrenal Cortex axis (HPA).

Activation of cortical and subcortical areas in the brain will generate the neural impulses that stimulates the hypothalamic neurons in the Paraventricular Nucleus to release CRH and AVP. CRH stimulates the anterior pituitary to release adrenocorticotrophic hormone that activates the adrenal gland cortex to release glucocorticoids. CRH also activates catecholaminergic neurons in the LC that stimulates the SNSAM to release noradrenaline and adrenaline (SANTOS & SPADARI-BRATFISCH, 2006). Glucocorticoids and catecholamines are considered the hall markers of stress since they play a pivotal role in the regulation of molecular and physiological stress reaction (FIGURE 1).

Despite of being originally related to many diseases, a new definition has emerged considering that stress also plays a positive role in the adaptation to new environments or situations as well as anticipation of future challenges as parts of our daily routine (LU et al., 2021). This positive stress was referred to as "eustress" in opposition to the "distress" (LU et al., 2021).

Selye (1936) proposed that the stress response occurs in three phases of what he called "General Adaptation Syndrome" (GAS). Upon the contact with the stressor, the organism displays the alarm reaction, described as the initial impact caused by the aggressive agent. On this phase, higher plasmatic levels of catecholamines and glucocorticoids improve catabolic mechanisms triggering the mobilization and properly distribution of energy to organs and tissues (VERAGO et al., 2001; FARIAS-SILVA et al., 2002; FIGURE 1). Those actions provide energy supplies for the decision to face or flee the threatening situation, the so-called “fight or flight reaction” (CANNON, 1935). After a period of contact with the aggressor, the organism starts adaptive mechanisms to reset homeostasis or to adapt to the new situation. The adaptation phase is characterized by the stimulation of anabolic processes in order to reestablish energy sources. Demands that do not exceed the organism adaptive capacity belong to physiological and behavioral responses are not considered stressors (KOOLHAAS et al., 2011).

However, when the adaptation does not happen and the contact with the aggressor is either too intense, prolonged or repeated, the organism enters the GAS third phase, characterized by exhaustion after the effort of an unsuccessful adaptation (SELYE, 1936; VAN DE KAR et al., 1991; HUETHER et al., 1999; CARRASCO & VAN DE KAR, 2003; McEWEN, 2005; RIBEIRO, 2012). In this phase, physiological and structural changes culminate in increased susceptibility to some diseases. Both acute and chronic stress can culminate in the exhaustion phase leading to functional potentially pathological changes.

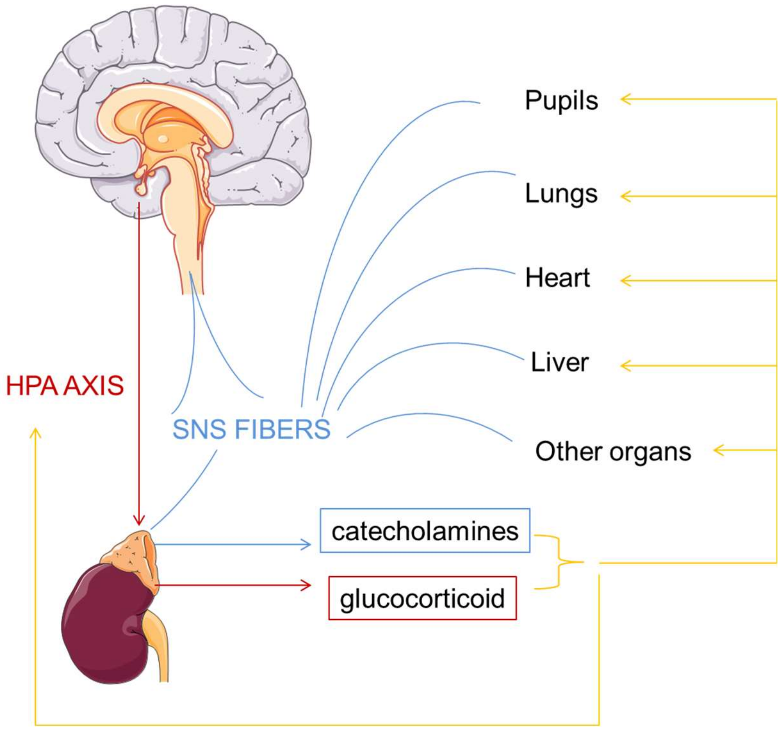

FIGURE 1: Schematic representation of stress response activation. The response begins in the brain with activation of sympathetic nervous system (SNS)-adrenal medulla (blue arrows and lines) and hypothalamus-pituitary-adrenal cortex axis (HPA axis, red arrows) with consequent secretion of catecholamines and glucocorticoids, respectively. SNS fibers also innervate the majority of the viscera where also release noradrenaline. Catecholamines and glucocorticoid orchestrate the peripheral physiological response to stress and also participate of the control of the response (orange arrows and lines).

Specificity of the stress response

In his theory, Selye (1936) defined stress as unspecific. However, currently it is assumed that the stress response results from the interaction between individual characteristics and environmental demands. The cognitive, behavioral and visceral aspects of the response to the stressor provide a better perception of the situation and its demands, as well as a fast processing of the available information, enabling the search for solutions, selecting appropriate behaviors and preparing the organism to act quickly and efficiently (McEWEN, 2000). Thus, the pool of neuroendocrine stress mediators released in each specific situation is determined by several factors such as age, gender, genetic pattern, or previous experience. Moreover, it also depends on the stressor characteristics, such as type, duration, intensity, and frequency of contact (SANTOS & SPADARI-BRATFISCH, 2006).

Therefore, considering that cognitive aspects and perceptions of stressors by each individual are determinant of the response (KOOLHAAS et al., 2011), in a group of several people exposed to the same stressful situation, each person may develop a different response. Even though, the consequences of stressful events in the initiation and progression of some diseases are clearly observed in the clinical and experimental research on stress (GLASER &

KIECOLT-GLASER, 2005; WIEDUWILD et al., 2020). Exposure to chronic mild stress activated hematopoietic stem cells proliferation in the mouse bone marrow, increasing the production of leukocytes and their amount in the blood (HEIDT et al., 2014). On the other hand, acute mental stress reduced the circulating levels of those cells in mouse and humans and activated endothelial cells, increasing leukocyte infiltrates in tissues such as the heart, lungs, skin, and atherosclerotic plaques (HINTERDOBLER et al., 2021). Increased circulating levels of inflammatory cytokines in the absence of pathogens, so-called sterile inflammation, has already been described in response to stressful events (reviewed by LEVINE, 2022).

Uncontrollability and unpredictability

Identifying the mechanisms through which stress converts from beneficial to harmful, or vice versa, is one of the goals of research in this area. Koolhaas and cols. (2011) proposed that stress becomes harmful when a cognitive perception of uncontrollability and/or unpredictability is expressed in physiological and behavioral responses. Unpredictability might be defined as the absence of an anticipatory response; uncontrollability is the loss of control in certain situation (KOOLHAAS et al., 2011). This emphasizes the importance of cognitive and perceptual aspects of stress for each individual, in addition to the typical neuroendocrine responses (KOOLHAAS et al., 2011).

Therefore, not only the physical nature of the stressor predisposes to exhaustion and pathology but rather the intensity in which the stimulus can be predicted and controlled (WEISS, 1972; KOOLHAAS et al., 2011). However, it is not the actual control that counts, but the perceived control (SALVADOR, 2005).

Moreover, controllability and predictability are generally defined as binary factors, i.e., full control or complete absence of control, often using strongly aversive stimulus. However, in everyday life situations controllability is graded from absolute control, via threat to control, to loss of control. In theory, this leads to a three-dimensional constellation in which controllability and predictability form two dimensions and the third dimension is stressor intensity.

Stress research at the BEST

For more than 30 years, the research group at the Laboratory of Stress Biology (Federal University of Sao Paulo) has investigated the effects of stress on behavioral, metabolic, endocrine and cardiac parameters in animal models (BASSANI & DE MORAES 1988; SPADARI-BRATFISCH et al., 1999; ORTOLANI et al., 2011; MOURA et al., 2017; SPADARI et al., 2018; CORDEIRO et al., 2020; DE CARVALHO et al., 2021; DE CARVALHO et al., 2022; CACERES et al., 2022; MOURA et al., 2022; MOURA et al., 2023).

Advances in the understanding stress mechanisms continue to be greatly benefited by animal models. They provide unique information about the physiology of stress, its signaling pathways and pathological consequences, which would be impossible to test in humans. Moreover, mechanistic studies in animal models have corroborated the stress-related pathophysiological changes in humans (MOURA et al., 2017; HINTERDOBLER et al., 2021)

The stress protocol of foot shock in rats has been used to investigate cardiovascular, endocrine and behavioral aspects of the stress response by our research group. It is a model of environmental stress characterized by psychological and physical stress, which is sub chronic, repeated, unpredictable and unescapable. Electric pulses of 1 mA intensity, 1 second duration are delivered at randomized intervals of 5 to 25 seconds. The rats are submitted to one daily session of stress during 30 minutes, for 3 consecutive days. It does not cause any paw lesion or locomotion alteration, reduction of food and liquid intake or body weight (ORTOLANI et al., 2011; MOURA et al., 2022). Interestingly, stressed rat's anxiety levels were lower than those seen in non-stressed rats (ORTOLANI et al., 2011). Immediately after the first stress session corticosterone plasma level, the main glucocorticoid in rodents, was higher than it was in non-stressed rats. However, immediately before the next stress session, the corticosterone level was similar in stressed and non-stressed rats, suggesting that the rats did not anticipate the stressful situation, what characterizes unpredictable stress (VERAGO et al., 2001). After the next two stress sessions, corticosterone levels were progressively higher. The stress induced increase in corticosterone level was attenuated when the rats had access to high caloric food, enriched with glucose and fat, the so-called “comfort food” (ORTOLANI et al., 2011).

Foot shock-stressed rats presented higher plasmatic levels of glucose and insulin than non-stressed rats (VERAGO et al., 2001; FARIAS-SILVA et al., 2002). Basal lipolysis was also higher in adipocytes isolated from stressed rats, presenting a lower sensitivity to insulin (FARIAS-SILVA et al., 2002). Those data indicate that this foot shock stress protocol promotes metabolic changes, consistent with energetic substrates mobilization.

The vast majority of the stress studies in the literature explores stress-mediated behavioral changes, focusing on the central nervous system and brain. However, as above mentioned, the stress response is characterized by being diffuse and potentially affecting other systems in the organism. Cardiovascular, immune, and gastrointestinal systems are highly affected by stress (CARNEVALE & LEMBO, 2018; OSBORNE et al., 2020; DE CARVALHO et al., 2021). Therefore, studies have shed light on the physiological consequences of the stress response in multiple systems simultaneously (ELENKOV et al., 2000; CARNEVALE & LEMBO, 2018).

Because the heart is a main target for the stress mediators, catecholamines and glucocorticoids, our research group has invested substantial efforts understanding the mechanisms triggered by stress on heart physiology.

Stress and the heart

Despite recent medical advances, cardiovascular diseases remain as the main cause of death in Brazil and in the rest of the world (DATASUS; WHO) and it is recognized that there is a correlation between psychological stress, several adverse cardiac events (ESCH et al., 2002; SANTOS & SPADARI-BRATFISCH, 2006; THEORELL et al., 2006; WITTSTEIN, 2008; RICE, 2012; STEPTOE & KIVIMAKI, 2012; MOURA et al., 2017; KIVIMAKI & STEPTOE, 2018; HINTERDOBLER et al., 2021) and the growing demand on health care systems (LEVINE, 2022). Natural disasters, outbreak of war, terrorist attack or even a sport competition as the FIFA World Cup are acute psychological stressors that are known to precipitate adverse cardiac events, such as sudden death, myocardial infarction and arrhythmia (reviewed by KIVIMAKI & STEPTOE, 2018; LEVINE, 2022).

A notable cardiac manifestation of acute stress is the stress cardiomyopathy, also called as Takutsubo cardiomyopathy. This myocardial syndrome is characterized by sudden abnormalities in the heart anatomy, electrical signal propagation, and left ventricle function (SUZUKI et al., 2014; LEVINE, 2022). Populational studies also associated chronic stressors with higher risk of cardiac events. Financial issues, work stress, marital stress and posttraumatic disorders are commonly linked to coronary heart disease (reviewed by LEVINE, 2022).

Those reports also suggest that psychological stress has a more relevant role not only as a trigger of cardiovascular diseases, but also related to accelerated disease progression and impaired recovery (KIVIMAKI & STEPTOE, 2018). In addition, it is important to emphasize that there is a strong association between stress and cardiovascular disease in patients with pre-existing cardiovascular disorders or in individuals at high cardiac risk (KIVIMAKI & STEPTOE, 2018). Despite many association studies, the underlying mechanisms whereby psychological stress contribute to and affect cardiac physiology remains uncomplete.

Heart is the contractile muscular organ that ensures blood supply to every cell into the body. The beating rate and the ability to develop force are crucial for its function. Although these characteristics are intrinsic to the myocardium, they are mainly, but not exclusively, under control of the autonomic nervous system. Compounds released by sympathetic neurons (mainly noradrenaline), adrenal gland medulla (adrenaline and noradrenaline), and the vagus nerves (acetylcholine) are accountable for the short-term modulation of cardiac performance. While catecholamines increase cardiac output through the positive effects on chronotropism, inotropism, and lusitropism, acetylcholine promotes the opposite through the negative effect on chronotropism (SANTOS & SPADARI-BRATFISCH, 2006; RIBEIRO, 2012).

In the target cells, catecholamines couple to specific membrane receptors, called adrenergic receptors, of two types: beta (β-AR) and alpha adrenoceptors (WOO & XIAO, 2012). β-ARs, the predominant adrenoceptor type in the cardiac cells, are expressed in three subtypes: β_1-AR, β_2-AR, and β_3-AR. All the three subtypes of β-ARs are G protein-coupled receptors (BYLUND, 1992; SANTOS & SPADARI-BRATFISCH, 2006; SPADARI et al., 2018).

Classically, β_1-AR and β_2-AR stimulation by their agonists activates the stimulatory G protein (Gs)-adenylyl cyclase (AC)-cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) signaling pathway (FIGURE 2). In cardiomyocytes, the phosphorylation of PKA substrates (BRODDE, 1991) mediates an increase in the calcium transient, heart rate, contraction force and relaxation rate, improving the cardiac output (FIGURE 2). PKA also phosphorylates other substrates, such as the nuclear factor-κB (NF-κB) and cAMP responsive element binding protein 1 (CREB1), that drive adrenergic-mediated gene regulation. PKA also phosphorylates β_1- and β_2-ARs. Phosphorylated β_2-ARs increase their affinity to inhibitory G protein (Gi) that promotes opposite effects in the AC-cAMP-PKA signaling pathway, avoiding adrenergic over-stimulation (SPADARI-BRATFISCH & SANTOS, 2008; WOO & XIAO, 2012; FIGURE 2).

Persistent adrenergic stimulation can trigger structural and functional changes in the cardiac β-AR population (SPADARI-BRATFISCH & SANTOS, 2008; FAJARDO et al., 2011). β_1-AR persistent stimulation has cardiotoxic effect through activation of apoptotic pathways, which promote impairment of cardiac remodeling (ENGELHARDT et al., 1999; BISOGNANO et al., 2000; ZHU et al., 2003). Differently, β_2-AR over stimulation activates cellular survival pathways, despite of some contractility impairment (ZHU et al., 2001; ZHANG et al., 2011). Changes in β-ARs expression and signaling are related to impairment in cardiovascular function induced by sympathetic overstimulation as it occurs in the failing and in the senescent heart (BRODDE, 1991; SPADARI et al., 2018). In heart failure and aging, β_1-AR expression is reduced, while β_2-AR expression is enhanced or unchanged (BRISTOW et al., 1986, BRISTOW et al., 1993). Increased β_2-AR/ β_1-AR ratio was also shown in some experimental stress models (SPADARI-BRATFISCH et al., 1999; MOURA et al., 2017; MOURA et al., 2022), when there is sympathetic overstimulation as well. Those data suggest that the modulation of the expression and function of the β_1-AR and β_2-AR might be part of adaptive mechanism aimed to protect the heart against the effects of adrenergic overstimulation.

In the animal model of foot shock stress there is a reduction in the atria response to β_1-AR agonists and an increase in the response to the β-AR non-selective agonist (isoprenaline) and to β_2-AR selective agonist (salbutamol) (BASSANI & DE MORAES, 1988; VANDERLEI et al., 1996; MOURA et al., 2017). Those changes are correlated to higher β_2-AR protein expression and lower β_1-AR protein expression in both atria (MOURA et al., 2017) and ventricles (CORDEIRO et al., 2020; MOURA et al., 2022), indicating that β_2-AR upregulation contributes to the enhanced cardiac response to catecholamines. Nevertheless, the stress-induced alterations in the β_1-ARs were seen in the heart of mice knockout for the β_2-ARs (MOURA et al., 2023). β_3-AR expression was unaltered in the heart of foot shock stressed rats (CACERES et al., 2022). Those stress-induced changes in cardiac β_1-AR and β_2-AR expressions and activity were transient. However, persistent changes were identified in some proteins of their intracellular signaling pathways, mainly those related to cardiomyocytes survival (CORDEIRO et al., 2020).

Additionally, using microarray technique, we have recently demonstrated that the alterations in the cardiac gene expression profile triggered by stress can be more extensive and that the profile of genes dysregulated by stress when β_2-AR was upregulated was completely different from that seen when β_2-AR was pharmacologically blocked. This suggests that β_2-AR modulates those stress-induced changes in the expression of several genes in the heart (DE CARVALHO et al., 2021). Therefore, although not essential for post-stress survival (MOURA et al., 2023), β_2-AR plays an important role in the cardiac stress response (DE CARVALHO et al., 2021). Furthermore, those results provide insight into the influence of stress in the cardiac cells phenotype (DE CARVALHO et al., 2021), probably with clear functional impairment. Further study of the genes and signaling pathways involved with the cardiac stress response may clarify the molecular mechanisms by which stress interfere in the heart physiology.

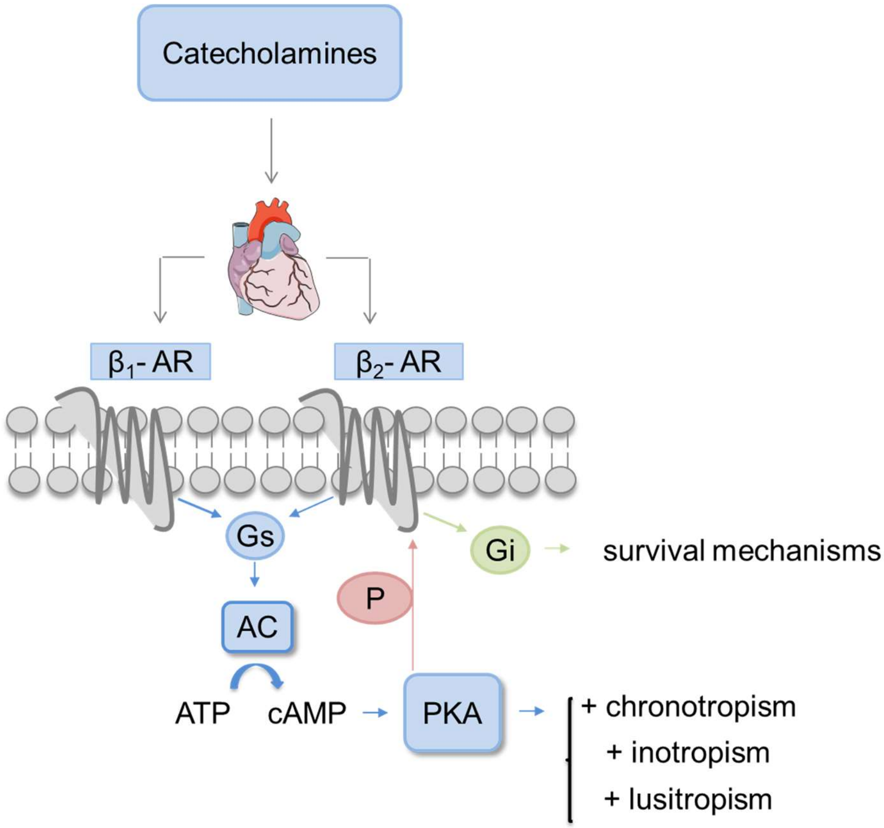

FIGURE 2: Schematic representation of primary catecholamines actions on cardiac betadrenoceptors (β-AR). Intracellular signaling of both β_1-AR and β_2-AR activates the stimulatory G protein (Gs)-adenylyl cyclase (AC)-cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) signaling pathway. Phosphorylation of PKA substrates increases chronotropism, inotropism and lusitropism in the

heart. PKA also phosphorylate β_2-AR increase their affinity to inhibitory G protein (Gi), which stimulate survival mechanisms.

So, the above-mentioned findings suggest that stress-induced changes in β-AR signaling might play a key role in the mechanisms that turn stress from an adaptive response aimed to guarantee survival into a deleterious one and a potential cardiovascular risk factor. Identifying the mechanisms that induce such alterations in the β-AR, may be important to clarify the pathophysiological processes related to stress, and also provide scientific basis for clinical interventions.

Concluding remarks

The accumulated knowledge presented here demonstrates that psychological stress events are able to induce deep physiological changes, as such extent that might precipitate the onset of diseases. The emerging evidences showed are consistent in adding stress as a relevant cardiovascular risk factor, as well as smoking, lack of regular physical activity, high blood-pressure and cholesterol levels, overweight, and others.

As above-mentioned, stress response includes triggering of central and peripheral physiological alterations but also depends on individual perception of the stressful situation. This improves the complexity of the identification and characterization of the stress mechanisms, particularly in humans.

We and others have invested substantial efforts to demonstrate the molecular and physiological mechanisms that support the indication of psychological stress as a cardiovascular risk factor. Understanding the molecular and pathological mechanisms involved in the stress response might help to definitely demonstrate how damaging stressful situations can be to our organism and life.

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Competing interests

The authors declare no competing interests.

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