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Review

Stressed brain, diseased heart: A review on the pathophysiologic mechanisms of neurocardiology

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ABSTRACT

Cardiovascular diseases are traditionally related to well known risk factors like dyslipidemia, smoking, diabetes and hypertension. More recently, stress, anxiety and depression have been proposed as risk factors for cardiovascular diseases including heart failure, ischemic disease, hypertension and arrhythmias. Interestingly, this association has been established largely on the basis of epidemiological data, due to insufficient knowledge on the underlying pathophysiologic mechanisms. This review will revisit evidence on the interaction between the cardiovascular and nervous systems, highlighting the perspective on how the central nervous system is involved in the pathogenesis of cardiovascular diseases. Such knowledge is likely to be of relevance for the development of better strategies to treat patients in a holistic perspective.

1. Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide, being responsible for almost 32% of all deaths in women and 27% in men in 2004 and expected to kill 23.4 million people by 2030 if current trends remain [1]. While elevated blood levels of cholesterol, hypertension, diabetes mellitus and smoking are well-known risk-factors for CVD [2], understanding how other factors contribute to this burden is essential to develop new strategies to combat and/or prevent it. Among these, the central nervous system (CNS), in particular the stress response seems to be of relevance in the pathogenesis of CVD.

This review focuses on neurocardiology, highlighting the effects of central circuits over the control of cardiovascular system and on how peripheral mediators acting on specific brain regions influence neurocardiac conditions.

2. Neurocardiology: the facts

Psychiatric and neurologic diseases are positively associated with CVD. Epidemiological data clearly suggests that depression is an independent risk factor for myocardial infarction (AMI) and heart diseases in general [3,4]. Prospective studies with depressed individuals showed that a history of a major depressive episode was associated with a higher risk of AMI, even after correction for major coronary risk factors [5–7]. Of interest, the same was observed for both men and women [7]. In fact, a meta-analysis of 11 longitudinal studies revealed that depression is associated with a 1.64 relative risk (ranging from 1.50 to 4.16 in original studies) for development of coronary heart disease (CHD) [8]. Unfortunately, most of the studies measured depression at a single time-point during the follow-up period, which precludes the analysis on how time of exposure to depression was associated with CHD.

The impact of depression is also important in patients with already established CHD. Long-term mortality was higher (cardiac and all-causes) in patients who presented depression on hospital admission and/or on follow up [9,10]. This outcome persisted, although less powerfully, after correction for socio-demographic and biobehavioral characteristics, use of antidepressants and CVD medications [10]. Interestingly, patients only with depression displayed a higher risk of mortality (OR 2.10) than those only with CHD (OR 1.67) while those with both conditions displayed an additive risk of mortality (OR 4.99) reinforcing the importance of affective disorders on CVD [10]. The consequence of depression on heart diseases extends to other conditions including sudden cardiac death [11,12] and heart failure (HF) [13,14]. Neurologic conditions are also implicated in the pathophysiology of several cardiac conditions: e.g. both acute stroke and epilepsy are associated with sudden death and de novo ECG alterations [15–18].

3. The relevance of stress in neurocardiology

Stress is a state of threatened homeostasis. For re-establishment of the equilibrium a repertoire of physiologic and behavioral responses

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is rapidly mobilized, constituting the adaptive stress response [19]. The adverse consequences of stress result from the inability of the individual to cope with the stressful stimuli or from maladaptive responses that may restore the homeostasis in short-term but may impose damage at different body systems in the long-term. It is a common belief that daily stressful situations predispose individuals to adverse cardiovascular events. The first reports of cardiac deaths related with stress date from 1942 Cannon's paper "voodoo death" in which the author suggested that an extreme condition of frighten inflicted to the victim might explain the multiple cases of tribal voodoo death [20]. Acute stress, elicited by natural disasters like earthquakes is likewise related with an increase in cardiac events and sudden death [21].

Takotsubo cardiomyopathy (or "stress cardiomyopathy") is probably the most remarkable example of how stress promotes direct heart injuries and will be discussed in further sections. More recently, the INTERHEART study investigated the associations of several psychosocial stressors with the risk of AMI [22]. This study compared 11,119 patients with a previous event of AMI with 13,648 patients free of clinical heart disease. Psychosocial stress was assessed by four simple questions about stress at work and at home, financial stress, and major life events in the past year; results estimated a 1.38 fold greater risk of AMI for patients who went through several periods of work stress and 2.14 for those who experienced periods of permanent stress at work [22].

In laboratory settings, the effects of chronic stress have been widely studied in rodents mainly using the chronic mild stress (CMS) model in which animals are exposed during 4 to 6 weeks to an unpredictable sequence of mild stressors [23]. CMS rodents not only display depressive-like behavior but also increased anxiety and impaired cognition, highlighting the fact that the co-morbid effects of human depression can also be observed in rodents [24]. Of notice, these animals present other anomalies, namely elevated heart rate (HR), reduced HR variability (HRV), elevated sympathetic tone and exacerbated cardiovascular reactivity when submitted to external stressors, suggesting that stress promotes an autonomic imbalance in favor of sympathetic system [25,26].

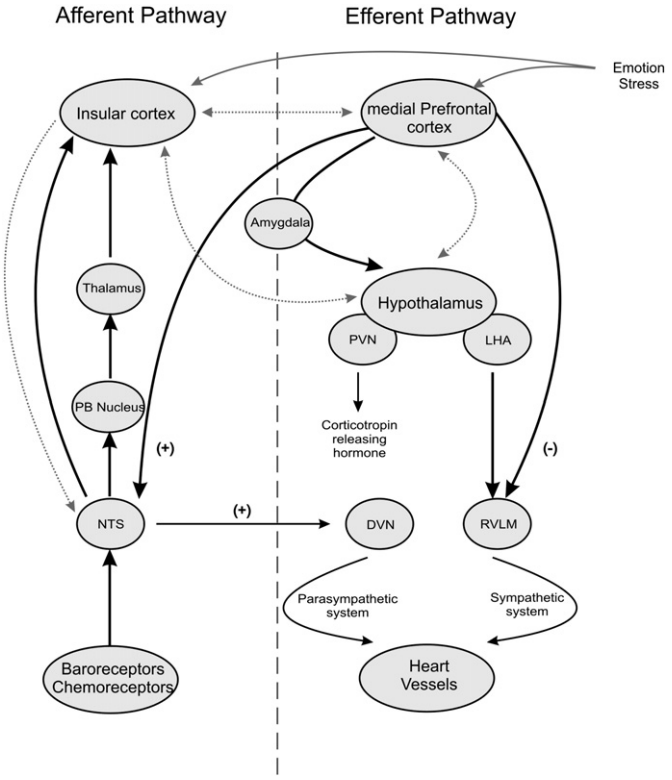

Fig. 1. Simplified schematic representation of the anatomical organization of autonomous nervous system in mammals. The regulation of sympathetic and parasympathetic systems involves a complex interaction between cortical and subcortical and medullary loci and peripheral organs. Apart from the more established efferent and afferent pathways (full lines), there are multiple interconnections between the different loci involved in the modulation of the autonomous nervous system (dot gray lines). In many cases their functional significance is still largely unknown but is likely to be relevant for the proper integration of the multiple inputs that control brain–periphery interactions. DVN-dorsal vagal nucleus; LHA-lateral hypothalamic area; NTS-nucleus of the solitary tract; PB-parabrachial; PVN-paraventricular nucleus; RVLM-rostroventral lateral medulla.

4. Neuronal networks implicated in cardiovascular regulation: the effects of stress

Cardiovascular regulation by CNS has been widely discussed in the literature. Cardiovascular function is regulated by the autonomic nervous system, which encompasses two major divisions: the sympathetic and the parasympathetic system; the appropriate balance (autonomic tone) between the two is fundamental to the pathophysiology of CVD.

The organization of the autonomic nervous system (Fig. 1) is complex (for a review see [27]). It is widely recognized that regulation of cardiac function is dependent on medullary centers, namely the nucleus of the solitary tract (NST) and the rostroventrolateral medulla (RVLM) [27,28]. While the former receives afferents from baroreceptors and the visceral sensorial information derived from cranial nerves (including the vagus), the RVLM is mainly composed by excitatory neurons that are responsible for the generation of the sympathetic response. Although these regions generate reflex responses that may orchestrate timing cardiac adaptations, it is now clear that cardiac regulation is also dependent on supramedullary regions.

The insular cortex (IC) is a critical area in controlling the parasympathetic and the sympathetic tones. Not surprisingly, middle cerebral artery stroke victims, with insular damage, are prone to cardiovascular sudden death and autonomic alterations [29]. Studies with synchronized electric stimulation in animal models uncovered a chronotropic map in the IC [30]. While pure tachycardia was produced by stimulation of the rostral posterior insula, bradycardia was produced from the caudal posterior insula. Interestingly, there is evidence for a lateralization of cardiac control in this brain region: while the sympathetic tone is predominantly regulated by right insular regions, parasympathetic cardiac manifestations are regulated by the left insula [31,32]. Clinical data collected in stroke patients showed that cardiac arrhythmia produced by unbalanced cardiac autonomic activity favoring the sympathetic system was more common after cerebral infarction on the right hemisphere [33]. Therefore the mechanism of cardiovascular instability following stroke seems to result from loss of the inhibition exerted by the right IC over inferior areas of cardiac control that predisposes to rhythm instability [34].

The involvement of the IC in stroke patients is easily documented by imaging methods; on the contrary, documenting a relation between stress and IC dysfunction, although important in light of the previous section, is not straightforward and is scarce [35]. Preliminary data in animals from our lab revealed that the IC is indeed a target of chronic stress (Pereira VH et al., unpublished observations).

The medial prefrontal cortex (mPFC) is a subdivision of the rodent's prefrontal cortex composed by several cortical areas (e.g. frontal area 2, dorsal and ventral anterior cingulate areas, prelimbic, infralimbic and medial orbital areas) [36]. Besides its implication in several cognitive functions [37] the mPFC is also involved in the regulation of cardiovascular functions [38,39]. The mPFC is a well-known target of stress. It has been shown that chronic stress leads to volume loss and dendritic atrophy of the mPFC; more prominently in the left hemisphere [36,37], which may, by decreasing left-to-right mPFC inhibition, cause an autonomic imbalance in favor of the sympathetic system. In this sense, the shift of a predominant parasympathetic tone in the normal functioning mPFC toward a predominant sympathetic tone in the "stressed" mPFC may be of major importance in the pathophysiology of