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Editorial

Stress, behavior and the heart

A broad spectrum of research, spanning epidemiological studies, clinical research, preclinical investigations and animal models, has pointed to a link between psychological factors and cardiovascular dysfunctional states.

Acute and chronic life stressors, psychological alterations such as anxiety and depression, personality traits such as anger and hostility, reactive behavioral coping strategies, as well as the absence of social support have all been shown to interfere with and modulate the onset and progression of cardiovascular alterations. These psychological elements, in many instances, appear to be independent risk factors of disease, as important as traditional ones such as cholesterol levels, waist fat, body mass index and poor physical activity.

Recently developed research approaches have shed light on the brain substrates, genetic and epigenetic factors, as well as cellular/molecular mechanisms that underlie the tight and complex relationship between stress, behavior and the cardiovascular system. However, despite a growing number of empirical investigations and accumulating clinical evidence, still several issues remain to be clarified about the mechanisms linking stressful events, psychological traits, behavioral coping and cardiovascular risk profiles.

This special issue is a collection of 19 selected review papers that present the newest scientific evidence in the multidisciplinary arena intersecting stress, behavior and the cardiovascular system. It gathers the contribution of leading scientists from a variety of disciplines (neuroscience, physiology, cardiology, pharmacology, psychology, epidemiology) who share a common interest in the complex interactions between the mind and the heart. A deeper understanding of such complex relationship cannot be achieved without a multipronged effort that includes basic science, preclinical research on animal models and human clinical and nonclinical studies. Moreover, the intricate interaction between genetic and environmental factors has to take into central account a lifecourse approach that includes early stages of development and the effect of epigenetic imprinting.

The paper by Eric Brunner focuses on the epidemiologic evidence about direct and indirect pathways from chronic stress to cardiovascular morbidity and mortality and underscores the fact that the stepwise gradient of higher cardiovascular risk with lower social status is accounted for in good part by social gradients in health behaviors (Brunner, 2017).

The review by Murray Esler examines the phenomenon of "triggered" heart disease, when the autonomic nervous system control of the heart by the brain goes awry, producing heart disease of sudden onset, precipitated by acute emotional upheaval, in the form of cardiac arrhythmias, myocardial infarction, Takotsubo cardiomyopathy and sudden death. The paper also comments on the evidence that chronic psychological stressors do have adverse cardiovascular consequences, for instance in the causal linkage of depressive illness to heart disease, and in the probable causation of atherosclerosis and hypertension by chronic mental stress (Esler, 2017).

Brenda Penninx's paper examines the mechanisms through which depression's burden of disease goes beyond emotional functioning and quality of life and extends to somatic health. Her paper reviews results from longitudinal cohort studies showing that depression, overall, increases the risk of cardiovascular morbidity and mortality of about 80%. According to her, the impact of major depressive disorder on cardiovascular health may be partly explained by mediating mechanisms such as unhealthy lifestyle (smoking, excessive alcohol use, physical inactivity, unhealthy diet, therapy non-compliance). Many biological pathways also play a role. The most relevant pathophysiological alterations, involving autonomic, HPA-axis, metabolic and immuno-inflammatory dysregulations are thoroughly presented and discussed (Penninx, 2017).

An interesting point of view concerning the psychological aspects of autonomic dysfunction and cardiovascular risk is that presented by Jos Brosschot and colleagues. These authors refer to the generalized unsafety theory of stress, which focusses on safety instead of threat and includes risk factors that have hitherto not been attributed to stress (Brosschot et al., 2017).

The paper by Viola Vaccarino and Douglas Bremner discusses important gender differences in both the frequency of psychosocial risk factors and their relationship with the risk of coronary heart disease. The authors provide evidence and comment on the fact that women have double the rates of stress-related psychiatric disorders, including PTSD and depression, compared to men, that these disorders are clearly associated with cardiovascular risk in women, and suggest that future studies should examine women in earlier developmental epochs in order to better understand mechanisms of disease and develop tailored intervention and prevention strategies. In particular, they suggest that psychosocial interventions, specifically designed to address women's stressors, could be the most helpful approach in the prevention and treatment of cardiovascular dysfunction in women (Vaccarino and Bremner, 2017).

Walker and colleagues discuss the importance of identifying appropriate biomarkers of resilience to psychological stressors,

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thus overcoming the bias represented by subjective reports. The authors provide a summary of the major concepts in the field of resilience, followed by a detailed critical review of the literature around possible physiological, neurochemical and immune markers. They conclude that in future experimental protocols, putative biological markers of resilience should be assessed both in baseline conditions and during controlled, laboratory stress challenges (Walker et al., 2017).

Sleep deprivation has become a relevant health problem in modern societies. Among its broad-ranging effects, sleep deprivation is capable of inducing neural autonomic control changes, increased oxidative stress, altered inflammatory and coagulatory responses and accelerated atherosclerosis. All these mechanisms link sleep deprivation and cardiovascular and metabolic disorders. Eleonora Tobaldini and colleagues provide an up-to-date review on this important topic (Tobaldini et al., 2017).

Given the intrinsic connection between the brain and the heart, a recent body of research also emerged with the aim of influencing cardiovascular system functioning by non-invasive brain stimulation (NIBS) methods such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation. Despite the therapeutic implications of cardiovascular activity modulation, such effects of NIBS have not yet been systematically reviewed. The aim of the work by Elena Makovac and colleagues was to meta-analyze studies on NIBS effects on blood pressure, heart rate and heart rate variability. Their results show that NIBS does indeed affect cardiovascular and autonomic nervous system activity, confirming a potential pathogenic brain-heart pathway to cardiovascular disease (Makovac et al., 2017).

The role of epigenetic mechanisms in the link between behavior and cardiovascular dysfunction is nicely exemplified in the paper by Khan and colleagues, where a specific condition (postural tachycardia syndrome, POTS) is analyzed. They focus their attention on the gene that encodes for the norephrine transporter (SLC6A2) and highlight the potential therapeutic application of strategies that target the epigenetic mechanisms implicated in the regulation of SLC6A2 expression in POTS (Khan et al., 2017).

Life stress has been associated with accelerated cellular aging and increased risk for developing aging-related diseases, including cardiovascual disturbances. However, the underlying molecular mechanisms remain rather elusive. A highly relevant process that may underlie this association is epigenetic regulation. In their review, Gassen and colleagues build upon existing evidence to propose a model whereby exposure to life stress, in part via its effects on the hypothalamic-pituitary axis and the glucocorticoid signaling system, may alter the epigenetic landscape across the lifespan and, consequently, influence genomic regulation and function in ways that are conducive to the development of aging-related diseases (Gassen et al., 2017).

Moving to preclinical studies involving animal models, this special issue includes a nice review paper by Myers and colleagues, where several brainstem nuclei are considered, which engage in autonomic control and therefore influence cardiovascular stress responsivity. In particular, this review focuses on the prominent brainstem monosynaptic inputs to the paraventricular hypothalamic nucleus, involving the periaqueductal gray, raphe nuclei, parabrachial nuclei, locus coeruleus, and nucleus of the solitary tract. Collectively, the study of these brain circuits in rodents represents an important avenue for delineating the complex interactions between stress and health (Myers et al., 2017).

Orexin, the arousal peptide, is the main character of Carrive's report. This neuropeptide originates from neurons located in an area of the dorsal hypothalamus well known for integrating defense responses and their cardiovascular component. Orexin neurons project to many regions in the brain, including those involved in cardiovascular control, as far down as sympathetic preganglionic neurons in the spinal cord. The present paper examines the link between orexin, stress and hypertension in rats, and maintains that orexin upregulation could be a factor in the development of essential hypertension, while orexin receptor antagonism has antihypertensive effects that could be of clinical use (Carrive, 2017).

The review by Wood and Valentino moves the focus to norepinephrine and the locus coeruleus-norepinephrine system as an important contributor to stress-induced cardiovascular disease. Interestingly, the authors examine the role of individual differences in behavioral coping strategies on cardiovascular vulnerability induced by social stress in rats. In fact, the establishment of different coping strategies and cardiovascular vulnerability during repeated social stress has recently been shown to parallel a unique plasticity in locus coeruleus afferent regulation, resulting in either excitatory or inhibitory inputs. This contrasting regulation of the LC would translate to differences in cardiovascular function modulation and may serve as the basis for individual differences in the cardiopathological consequences of social stress. The advances described suggest new directions for developing treatments and/or strategies for decreasing stress-induced cardiovascular vulnerability (Wood and Valentino, 2017).

Expanding the issue of individual differences in stress coping for health and disease, De Boer and colleagues underscore the importance of understanding the neural embedding of coping style variation. This review outlines individual differences in trait-aggressiveness as an adaptive component of the natural sociobiology of rats and mice, and highlights that these reflect the general style of coping that varies from proactive (aggressive) to reactive (docile). The authors propose that this qualitative coping style can be disentangled into multiple quantitative behavioral domains, e.g., flexibility/impulse control, emotional reactivity and harm avoidance/reward processing, each encoded into selective neural circuitries. They also suggest that, since functioning of all these brain circuitries rely on fine-tuned serotonin signaling, autoinhibitory control mechanisms of serotonergic neuron (re)activity are crucial in orchestrating general coping style. Thus, it is reasonable to believe that by untangling the precise neuromolecular mechanisms of different coping styles, we could provide a road map for developing better therapeutic strategies of stress-related diseases (de Boer et al., 2017).

Serotonin plays a specific modulatory role in cardiovascular stress responsivity, due to its well- known central control of the autonomic nervous system (ANS). The nucleus tractus solitarii (NTS) in the medulla is an area of viscerosomatic integration innervated by both central and peripheral serotonergic fibers. In particular, the NTS is the central zone with the highest density of serotonin 3 (5-HT3) receptors. In this review by Sevoz-Couche and Brouillard, evidence is presented that 5-HT3 receptors in the NTS of rats play a key role in one of the crucial homeostatic responses to acute and chronic stressors: the inhibitory modulation of the parasympathetic component of the ANS. The possible functional interactions of 5-HT3 receptors with GABAA and NK1 receptors in the NTS are also discussed (Sévoz-Couche and Brouillard, 2017).

The paper by Shively and colleagues also deals with serotonin, namely on the effects of serotonin re-uptake inhibitors (drugs which are widely prescribed for a number of disorders in addition to depression) on primate cardiovascular disease, behavior, and neuroanatomy. In particular, this paper focuses on the multisystem effects of sertraline treatment on adult female cynomolgous monkeys, a primate species shown to be a useful model for both depression and coronary and carotid artery atherosclerosis. Sertraline does not seem to have effects on depressive behavior, but it is shown to reduce anxious behavior, increase affiliation, reduce aggression, change serotonin neurotransmission and volumes of neural areas critical to mood disorders, and exacerbate coronary and carotid atherosclerosis. According to the authors, these data

suggest that a conservative approach to prescribing SSRIs for cardiovascular or other disorders for long periods should be explored (Shively et al., 2017).

The endocannabinoid system has also been implicated in the regulation of stress, emotional behavior and cardiovascular function. Preclinical findings indicate that the endocannabinoid anandamide modulates physiological and behavioral stress responses and may also protect the heart from arrhythmias. Moreover, recent experimental studies suggest that pharmacological enhancement of anandamide signaling via inhibition of its degrading enzyme fatty acid amide hydrolase (FAAH) exerts anxiolytic- and antidepressive-like effects and improves cardiac autonomic function and the electrical stability of the myocardium in rodent models that reproduce aspects of human psychological/cardiac comorbidity. In the review by Carnevali et al., the authors summarize and discuss such experimental findings, which might guide future preclinical studies towards a systematic evaluation of the therapeutic potential of pharmacological approaches that target FAAH activity for the treatment of the comorbidity between psychological disorders and cardiac disease (Carnevali et al., 2017).

The last two papers composing this special issue deal with two crucial ontogenetic phases, namely childhood and adolescence. Emerging epidemiological data strongly support that stress experiences during childhood and adolescence represent an independent risk factor for cardiovascular disease in adulthood. Experimental animal models of chronic behavioral stress during early postnatal life (specifically maternal separation) and adolescence provide a suitable tool to elucidate potential underlying biological substrates. The reviews by Murphy and colleagues and by Crestani highlight current putative molecular mechanisms based on evidence from rodents and support the prospective value of further investigations, which could help identify appropriate therapies to mitigate the long-lasting cardiovascular consequences of adverse emotional situations that occur before adulthood (Murphy et al., 2017; Crestani, 2017).

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