Neuroscience and Biobehavioral Reviews 74 (2017) 393–400

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

The brain norepinephrine system, stress and cardiovascular vulnerability

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ARTICLE INFO

Article history:
Received 20 January 2016
Received in revised form 22 April 2016
Accepted 22 April 2016
Available online 27 April 2016

Keywords:
Locus coeruleus
Norepinephrine
Social defeat
Coping
Cardiovascular disease
Susceptibility
Individual differences

ABSTRACT

Chronic exposure to psychosocial stress has adverse effects on cardiovascular health, however the stress-sensitive neurocircuitry involved remains to be elucidated. The anatomical and physiological characteristics of the locus coeruleus (LC)-norepinephrine (NE) system position it to contribute to stress-induced cardiovascular disease. This review focuses on cardiovascular dysfunction produced by social stress and a major theme highlighted is that differences in coping strategy determine individual differences in social stress-induced cardiovascular vulnerability. The establishment of different coping strategies and cardiovascular vulnerability during repeated social stress has recently been shown to parallel a unique plasticity in LC afferent regulation, resulting in either excitatory or inhibitory input to the LC. This contrasting regulation of the LC would translate to differences in cardiovascular regulation 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.

Contents

1. Introduction

The cardiovascular response to psychosocial stress, resulting in transient increases in blood pressure and heart rate, is functional in the acute sense. However, there is overwhelming evidence that chronic stress has adverse effects on cardiovascular health. Epidemiological studies such as INTERHEART revealed that those who reported "permanent stress" at work or at home were more than two times more likely to suffer from a myocardial infarction (Rosengren et al., 2004). Furthermore, marital stress was associated with a nearly 3-fold increased risk of coronary artery disease (Orth-Gomer et al., 2000). The association between stress and cardiovascular disease is unmistakable and can be replicated in preclinical animal studies, however the stress-sensitive

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http://dx.doi.org/10.1016/j.neubiorev.2016.04.018
0149-7634/

neurocircuitry that contributes to increased cardiovascular disease risk remains to be elucidated.

One system that has been implicated in the association between stress and cardiovascular disease is the brain norepinephrine (NE) system that arises from the pontine nucleus, locus coeruleus (LC). This review begins with an introduction to the anatomical and physiological characteristics of the LC-NE system that position it to be a major stress response system. Evidence that the LC processes cardiovascular information and in turn can impact cardiovascular function are discussed. Because social stress is most relevant for humans, this review focuses on cardiovascular vulnerability produced by social stress as predicted by the rodent resident-intruder model and the role of the LC-NE system in cardiovascular vulnerability in that model. A major theme highlighted in this review is that individual differences in coping strategy determine individual differences in social stress-induced cardiovascular vulnerability. Moreover, the recent discovery that the establishment of different coping strategies and cardiovascular vulnerability during repeated stress is paralleled by a unique plasticity in LC afferent regulation is discussed. The advances described suggest new directions for developing treatments and/or strategies for decreasing stress-induced cardiovascular vulnerability.

2. The locus coeruleus-norepinephrine stress response system

The hallmark of stress is generally considered to be activation of the hypothalamic–pituitary–adrenal (HPA) axis, with plasma glucocorticoid levels serving as the endpoint of that activation. However, sustained activation of the brain NE system may also be considered a hallmark of stress in that it is initiated by many of the same challenges in parallel with the HPA axis. Given its physiological attributes and connectivity, activation of the LC-NE system during stress has been suggested to serve as an arousal and cognitive limb of the stress response. Evidence discussed below however, underscores cardiovascular consequences of stress-related activation of the brain norepinephrine system. The coordination of cardiovascular and cognitive responses to stress may underlie co-morbidity of cardiovascular and affective symptoms of stress-related disorders.

2.1. Anatomical features of the LC-NE system

The pontine nucleus, LC is a primary source of norepinephrine in brain (Grzanna and Molliver, 1980; Swanson and Hartman, 1976). Recent studies using novel, selective tract tracing tools have refined our knowledge of the topography of LC neurons with respect to their afferent inputs and efferent projections (Robertson et al., 2013; Schwarz and Luo, 2015). However, for the most part the nucleus is still characterized by its homogeneous expression of norepinephrine in all neurons and its widespread, highly collateralized projection system that is a major source of NE in the forebrain (Aston-Jones et al., 1995; Swanson and Hartman, 1976). Notably, the LC serves as the primary source of NE in forebrain regions such as the hippocampus and cortex that govern cognition, memory and complex behaviors. With regard to cardiovascular function, the LC exerts both indirect (via the nucleus ambiguus (Amb)-rostroventrolateral medulla (RVLM) circuit) (Jones and Yang, 1985; McKitrick and Calaresu, 1996) and direct projections to the preganglionic sympathetic neurons within the intermediolateral nucleus of the spinal cord, a common pathway for stress induced cardiovascular responses (Jones and Yang, 1985; Spyer, 1992). Furthermore, there is clear evidence for projections from the LC to the central nucleus of the amygdala (CNA), another stress-sensitive brain region with cardiovascular impact (Kravets et al., 2015; Mason and Fibiger, 1979). Tract tracing studies have also provided evidence for LC projections to the medial part of the rostral dorsal motor vagal nucleus (DMV) and lateral part of the intermediate DMV, the location of preganglionic parasympathetic cardiac neurons (Ter Horst et al., 1991). Consistent with this, LC neurons are transsynaptically labeled from the heart (Standish et al., 1995). Evidence discussed below support the idea that LC exerts an inhibitory regulation on cardiac parasympathetic neurons and excitatory regulation on preganglionic sympathetic neurons.

Sources of LC afferents have been debated as a result of differences in retrograde tracers and whether the injection was limited to the cell body region (Aston-Jones et al., 1991). Because the dendrites of LC neurons can extend for several hundred microns outside of the nuclear zone, neurons with axons terminating in pericoerulear areas can synaptically contact LC dendrites and impact on LC activity although they may not be labeled by injections into the nuclear LC (Shipley et al., 1996). As a result, studies that limit retrograde tracers to the LC nucleus reveal a very limited number of afferents that include the dorsal cap of the paraventricular hypothalamic nucleus, the nucleus prepositus hypoglossi and nucleus paragigantocellularis (PGi) in the ventrolateral medulla (Aston-Jones et al., 1990). Because the PGi is a source of inputs to the preganglionic sympathetic neurons it is positioned to coordinate peripheral sympathetic activity with central noradrenergic activity (Van Bockstaele and Aston-Jones, 1995). The PGi is a major source of enkephalinergic innervation of the LC (Drolet et al., 1990). The importance of this input in stress-coping strategy and stress-related cardiovascular vulnerability is discussed below. In contrast to the restricted number of LC afferents identified by tracer injections limited to the nucleus LC, injections of retrograde tracers in pericoerulear regions where LC dendrites extend, combined with anterograde labeling from putative afferents and electron microscopy to verify synaptic connections reveal relatively numerous LC afferents (Luppi et al., 1995; Van Bockstaele et al., 2001; Van Bockstaele et al., 1998; Van Bockstaele et al., 1999). Of these, the central nucleus of the amygdala is relevant to cardiovascular function and as discussed below conveys cardiovascular-related information to the LC (Curtis et al., 2002). This is also a major source of the stress-related neuropeptide, corticotropin-releasing factor (CRF), afferents to the LC and a primary route through which stressors activate the LC-NE system (Curtis et al., 2002; Van Bockstaele et al., 1998).

2.2. Physiological characteristics of LC neurons

The rate and pattern of LC neuronal discharge have implicated the LC-NE system in the regulation of arousal and attention (Aston-Jones and Bloom, 1981a,b; Aston-Jones and Cohen, 2005; Foote et al., 1980; Williams and Marshall, 1987). LC neurons fire spontaneously and their rate of discharge correlates positively with the state of arousal (Aston-Jones and Bloom, 1981a; Foote et al., 1980). This relationship is more than correlation as selective chemical activation or inhibition of LC neurons is sufficient to impact on cortical and hippocampal network activity, indicating a degree of causality between LC discharge rate and forebrain indices of arousal (Berridge and Foote, 1991; Berridge et al., 1993). Notably, LC activation has been demonstrated to be necessary for cortical activation by stimuli including hypotensive stress (Page et al., 1993; Lechner et al., 1997) (see below). Thus, this is a route by which autonomic challenges can affect cortical functions.

In addition to rate, the pattern of LC neuronal firing is relevant to behavior. LC neurons fire in both a tonic and a phasic pattern with the latter characterized by synchronous bursting. Salient sensory stimuli elicit a burst of LC discharge that typically precedes orientation to the eliciting stimuli (Aston-Jones and Bloom, 1981b; Foote et al., 1980). This feature of LC neurons has suggested that