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THE DORSOMEDIAL HYPOTHALAMUS AND THE CENTRAL PATHWAYS INVOLVED IN THE CARDIOVASCULAR RESPONSE TO EMOTIONAL STRESS

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Abstract—Psychological stress elicits increases in sympathetic activity accompanied by a marked cardiovascular response. Revealing the relevant central mechanisms involved in this phenomenon could contribute significantly to our understanding of the pathogenesis of stress-related cardiovascular diseases, and the key to this understanding is the identification of the nuclei, pathways and neurotransmitters involved in the organization of the cardiovascular response to stress. The present review will focus specifically on the dorsomedial hypothalamus, a brain region now known to play a primary role in the synaptic integration underlying the cardiovascular response to emotional stress.

Key words: dorsomedial hypothalamus, stress, cardiovascular system, central pathways.

Contents

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Abbreviations: BMI, bicuculline methiodide; BP, blood pressure; DMH, dorsomedial hypothalamus; DMN, dorsomedial hypothalamic nucleus; HR, heart rate; l/dlPAG, lateral/dorsolateral region of PAG; NTS, nucleus tractus solitarius; PAG, periaqueductal gray region; PVN, paraventricular nucleus; RPa, raphe pallidus; RVLM, rostral ventrolateral medulla.

STRESS: IMPACT ON THE CARDIOVASCULAR SYSTEM

Psychological stress elicits increases in sympathetic activity that result in changes in the level of cardiac function and vascular resistance with consequent redistribution of blood flow. This physiological strategy enhanced the probability of survival for mammals faced with a physical threat in nature. However, with one-half of the world's population living in the cities (Ginkel, 2008), the impact of psychosocial stress has undoubtedly been a challenge for the cardiovascular system and body homeostasis. Indeed, psychological stress is considered a component of the so called cardiovascular risk (Lloyd-Jones et al., 2009), and examples of such stressors in modern society are numerous. Mittleman and colleagues reported that the relative risk of acute myocardial infarction in the 2 h after an episode of anger was more than double compared with no anger (Mittleman et al., 1995). The number of sudden deaths resulting from cardiac causes sharply increased on the day of the Northridge earthquake that struck the Los Angeles area in 1994 (Leor et al., 1996). Signs of elevated sympathetic activity are commonly observed in patients with white coat hypertension (Smith et al., 2004), a phenomenon in which patients exhibit elevated blood pressure (BP) that is likely a consequence of increased anxiety in a clinical setting. These examples illustrate the potential contribution of emotional stress in precipitating adverse cardiovascular events.

According to the reactivity hypothesis, persistently exaggerated psychological stress responses might be a marker of individuals or subgroups with increased risk of cardiovascular disease (Lovallo and Gerin, 2003). Although the potential causes of the individual differences in reactivity remain poorly understood, the possibility that prolonged stress might cause perpetuated changes in critical groups of neurons in the CNS, resulting in sympathetic overreactivity, overactivity or autonomic imbalance is plausible. Thus, to understand how psychological stress affects the cardiovascular system, it is necessary first to identify the nuclei involved and the central pathways that control the cardiac and vascular sympathetic outflows. The present brief review summarizes our current understanding of a central circuit that integrates the cardiovascular response to acute stress. The focus is the region of dorsomedial hypothalamus (DMH), which plays a key role within this circuit.

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DMH: ANATOMICAL ORGANIZATION

As functional studies involving the human hypothalamus are rare, comparison of the structural organization of the human hypothalamus with the hypothalamus of other species could provide a meaningful reference for extrapolating physiological findings obtained in studies involving hypothalamus of experimental animals to humans. In this regard, the human hypothalamus is now known to be significantly more homologous to the hypothalamus of the rat than was previously thought, and this seems to be particularly true regarding the DMH (Koutcherov et al., 2003, 2004). In this review, we refer to DMH to indicate a region of the hypothalamus that includes the dorsomedial hypothalamic nucleus (DMN) but also adjoining areas, particularly dorsal and posterior to the nucleus itself as well as laterally including the medial part of the perifornical area. In the rat, the DMH lies adjacent to the third ventricle, caudal and ventral to the hypothalamic paraventricular nucleus (PVN), dorsal to the ventromedial hypothalamic nucleus (VMH) and ventral to the mamillothalamic tract. Laterally, the DMH is bounded by the fornix and the lateral hypothalamic area (Fig. 1). Its caudal border is far less distinct and is loosely delimited with the posterior hypothalamic area. The DMN itself is subdivided in two distinct portions, a poorly defined diffuse portion and a cell dense compact portion or zona compacta (Paxinos and Watson, 1986), the latter being clearly delimited in the posterior part of the DMH. Since this subcompartmental organization is homologous to that found in monkeys and humans (Koutcherov et al., 2004), the DMH seems to be highly conserved during the course of the mammalian evolution. This observation fuels speculation that the same may be true for its functional role in the cardiovascular response to emotional stress.

DMH: A KEY REGION IN THE CARDIOVASCULAR RESPONSE TO STRESS

The DMH plays a key role in coordinating the neuroendocrine, autonomic and behavioral responses to emotional stress (DiMicco et al., 2002). Similarly, the DMH has also been implicated as a key component of the “panic circuit”. Chronic disruption of GABAergic inhibition in the DMH leads to panic-like responses in rats (Johnson and Shekhar, 2006; Shekhar et al., 2006). In the pioneering exper-

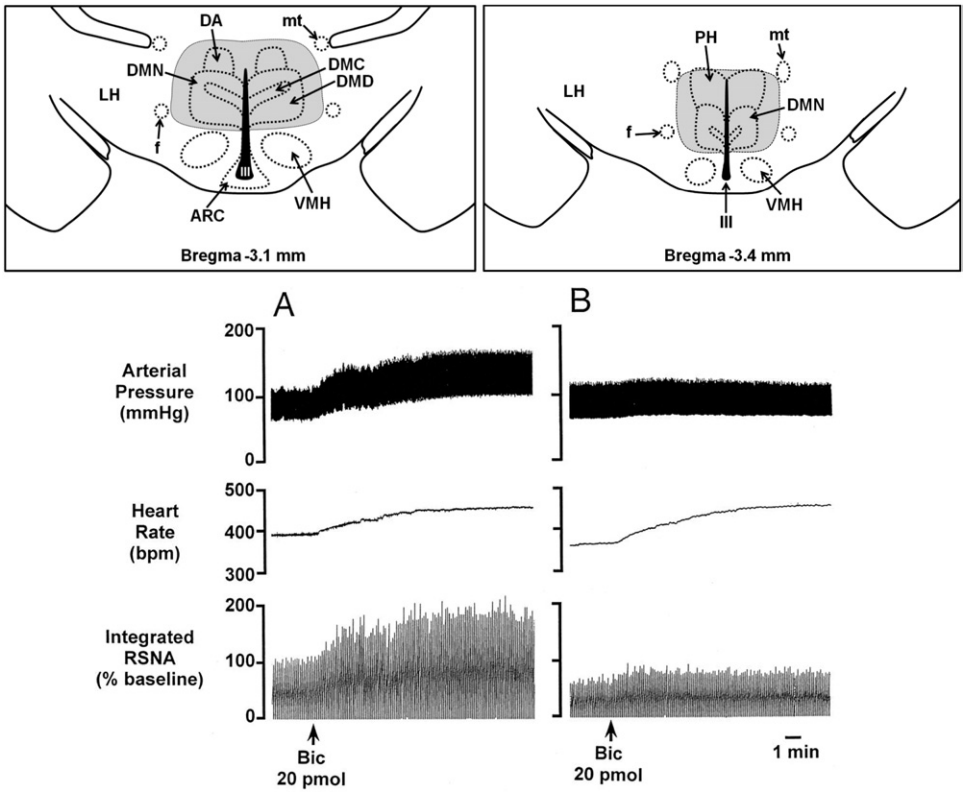

Fig. 1. Upper panel: Gray shading indicates the dorsomedial hypothalamus as referred in this review (3.1–3.4 mm posterior to Bregma according to atlas of Paxinos and Watson, 1986). Bottom panel: Example of the cardiovascular response evoked by microinjection of bicuculline methiodide into a site in the dorsomedial hypothalamic nucleus before (A) and after (B) unilateral microinjection of muscimol (1 nmol) into the rostral ventrolateral medulla pressor region (Fontes et al., 2001). Phenylephrine was infused continuously after the bilateral injections of muscimol to maintain baseline arterial pressure close to the control level. Note that after bilateral inhibition of the RVLM, bicuculline injection into the dorsomedial hypothalamic nucleus still evokes a tachycardic response, whereas the renal sympathetic and vasomotor responses are completely abolished. 3V, third ventricle; DMN, dorsomedial hypothalamic nucleus; DMC, compact portion of dorsomedial hypothalamic nucleus; DMD, diffuse portion of the dorsomedial hypothalamic nucleus; PH, posterior hypothalamic area; VMH, ventromedial hypothalamic nucleus; f, fornix; mt, mamillothalamic tract; LH, lateral hypothalamus; DA, dorsal hypothalamic area; ARC, arcuate hypothalamic nucleus. Bottom panel taken from Fontes et al., 2001, Am J Physiol Heart Circ Physiol. Am Physiol Soc, used with permission.