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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-

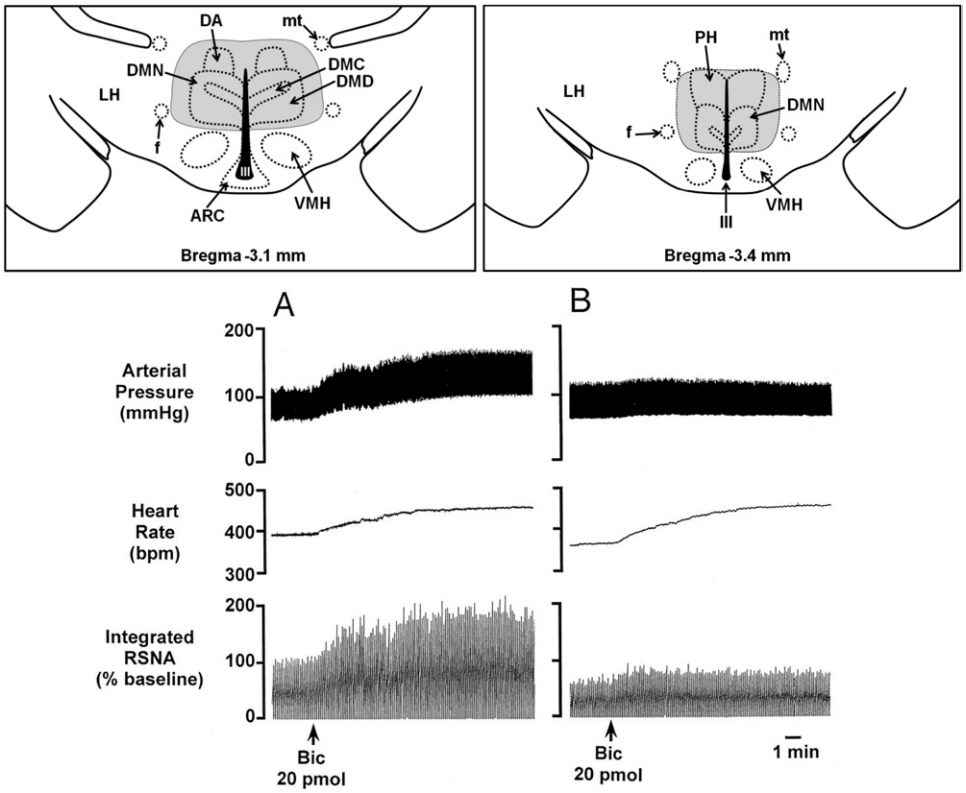

Fig. 1. Upper panel: Gray shading indicates the dorsomedial hypothalamus as referred in this review (3.1–3.4 mm posterior to Bregma according to atlas of Paxinos and Watson, 1986). Bottom panel: Example of the cardiovascular response evoked by microinjection of bicuculline methiodide into a site in the 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.

iments demonstrating a crucial role of DMH neurons in the cardiovascular response to acute stress, Lisa and colleagues (Lisa et al., 1989a) demonstrated that inhibition of DMH neurons with the $GABA_A$ agonist, muscimol, failed to influence baroreflex-induced tachycardia but abolished the increases in heart rate (HR) normally seen in an air stress paradigm (Lisa et al., 1989a). The site of action for muscimol was demonstrated to be specifically the DMH and not the paraventricular nucleus, another region potentially involved in the physiological responses to stress (Stotz-Potter et al., 1996b).

Conversely, DiMicco and colleagues demonstrated that microinjection of bicuculline methiodide (BMI), a $GABA_A$ receptor antagonist, into the DMH of conscious rats evokes marked increases in heart rate and pressor responses in conscious rats in a pattern that mimics the cardiovascular response to emotional stress (DiMicco et al., 2002). Thus, DMH neurons are under powerful GABAergic inhibition. Injections of BMI at doses ranging from 0.1 to 40 pmol that targeted the region of DMH evoke dose-related increases in mean arterial pressure (MAP), HR and renal sympathetic nerve activity (Horiuchi et al., 2004b). Moreover, injections of excitatory aminoacids (EEA) into the DMH also produce increases in HR and blood pressure (Soltis and DiMicco, 1991a, 1992; De Novellis et al., 1995). In addition, blockade of EEA receptors in the DMH suppresses the cardiovascular response evoked by BMI injections into the same region (Soltis and DiMicco, 1991b). These findings suggest that the response caused by blockade of GABAergic inhibition in the DMH of the rat is dependent on activation of local EAA receptors.

Although several studies have reported that disinhibition or excitation of DMH neurons can produce changes in blood pressure or heart rate similar to the ones seen during emotional stress, the precise location of these sites were not well characterized. Nonetheless, Samuels and colleagues (2004) have shown that injections (2 pmol/5 nl) of BMI into a specific area, dorsal to the DMN, called dorsal hypothalamic area (DA, Fig. 1) evoke increases in HR that are significantly greater than the increases observed after injection into the DMN itself (Samuels et al., 2004). They have also observed that the site of these injections corresponded to the location of neurons which project directly to the RP, which has been shown to be fundamental to the tachycardia evoked during stress (Zaretsky et al., 2003b). These data were later confirmed by Tanaka and McAllen (2008), who demonstrated that injections of D,L-homocysteic acid (50 mM in 15 nl) in the DA and dorsal parts of the DMN produced increases in heart rate, however, injections in the ventral parts of the DMN did not change it (Tanaka and McAllen, 2008). On the other hand, increases in blood pressure could be achieved by activating different areas of the DMH. Hence, even with high spatial resolution data, it is still not possible to determine the exact sites responsible for the changes in specific physiological variables evoked by DMH (or DA) activation.

It could be speculated that during acute psychological stress, the sensory input from the environment overcomes or reduces the tonic inhibition of neurons in the DMH, resulting in a characteristic cardiovascular response. Although the DMH receives inputs from several forebrain regions including amygdala (Soltis et al., 1998), that play roles in the physiological responses to stress (Fig. 2), the origin of the GABAergic input to neurons in the DMH remains unknown. The medial preoptic area (mPOA) may represent a significant source of inhibitory tone to key neurons in the DMH (Hunt et al., 2010). Another possibility is the medial prefrontal cortex (mPFC) which is a limbic structure involved in the regulation of cognitive and emotional information (Bush et al., 2000) and in the regulation of stress-induced neural activity (Amat et al., 2005). The DMH also receives projections from neurons in the mPFC, specifically in the infralimbic division (Hurley et al., 1991; Vertes, 2004). However, the only two functional studies offering a clue about a possible mPFC-DMH inhibitory projection contain divergent findings (McDougall et al., 2004; Radley et al., 2009).

ROSTRAL VENTROLATERAL MEDULLA AND THE VASOMOTOR COMPONENT OF THE RESPONSE TO ACTIVATION OF THE DMH

In the past decade, much has been learned about the descending pathways that mediate the sympathoexcitatory response evoked from the DMH. Previous anatomic studies indicated that the DMH contains no or very few neurons that project directly to the spinal cord (ter Horst and Luiten, 1986; Hosoya et al., 1987; Thompson et al., 1996). Therefore, the descending sympathoexcitatory pathway from the DMH should include one or more synaptic connections in supraspinal regions, such as the rostral ventrolateral medulla (Fontes et al., 2001), since this brainstem region contains sympathetic premotor neurons involved in the maintenance of vasomotor sympathetic activity and blood pressure (Dampney et al., 2000). The pressor and sympathoexcitatory responses, but not the tachycardic response evoked by activation of neurons in the DMH with BMI were greatly reduced after bilateral microinjection of muscimol into the rostral ventrolateral medulla (Fig. 1B). Thus, as shown in Fig. 2 (pathway 7), the vasomotor component of the response evoked from DMH is dependent on neuronal activity in the rostral ventrolateral medulla (RVLM) (Fontes et al., 2001). Indeed, in response to activation of the DMH, the firing rate of RVLM neurons could be increased by as much as 400% (Horiuchi et al., 2004b).

RAPHE PALLIDUS AND THE CARDIAC COMPONENT OF THE RESPONSE TO ACTIVATION OF THE DMH

The findings discussed above suggested that the pathway mediating the cardiac stimulation evoked by activation of the DMH was independent of the RVLM (Fontes et al., 2001). A search for the synaptic relay mediating the increase in heart rate caused by activation of DMH led to the raphe pallidus (RPa) as a potential candidate. Neurons in the RPa send direct projections to the upper thoracic intermediolateral cell column at those levels containing car-

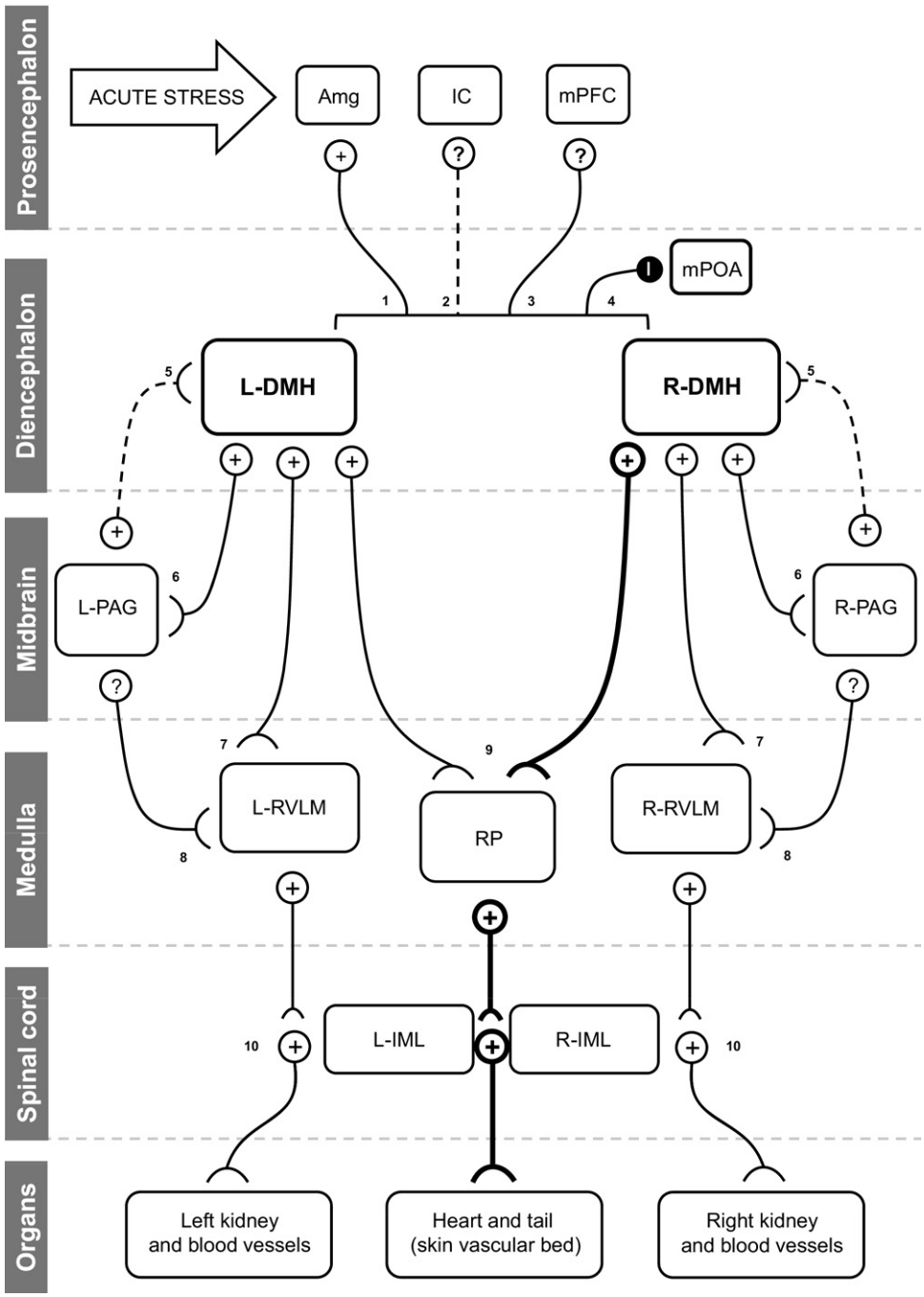

Fig. 2. Schematic diagram based on functional and anatomic studies showing descending pathways involved in the organization of the cardiovascular response to emotional stress at different levels of the neuraxis. The DMH is showed as a key integrative region in this response (Lumb, 1990; Thompson and Swanson, 1998; DiMicco et al., 2002), which also involves higher and lower brain regions (Kober et al., 2008; Cechetto and Shoemaker, 2009). From the DMH, descending pathways are represented bilaterally to better illustrate our recent functional findings and hypothesis (see text for details). 1—Amygdala/DMH (Nalivaiko and Blessing, 2001; Quirk and Gehlert, 2003; Quirk et al., 2003); 2—Insular cortex/DMH (Cechetto and Chen, 1990; Oppenheimer and Cechetto, 1990; Yasui et al., 1991; Butcher and Cechetto, 1998); 3—Medial prefrontal cortex/DMH (Vertes, 2004, 2006; Hoover and Vertes, 2007); 4—Medial preoptic area/DMH (Okamura et al., 1990; Zaretskaia et al., 2003; Yoshida et al., 2009; Hunt et al., 2010); 5 and 6—Periaqueductal gray/DMH and vice-versa (da Silva et al., 2003, 2006; de Menezes et al., 2006, 2008, 2009; Horiuchi et al., 2009; Villela et al., 2009); 7—DMH/rostral ventrolateral medulla (Fontes et al., 2001; Cao et al., 2004); 8—Periaqueductal gray/rostral ventrolateral medulla (Hudson and Lumb, 1996; Farkas et al., 1998); 9—DMH/raphe pallidus (Hosoya et al., 1987; Nalivaiko and Blessing, 2001; Zaretsky et al., 2003b; Horiuchi et al., 2004b; Samuels et al., 2004); 10—Rostral ventrolateral medulla and raphe pallidus/spinal cord/target organs (Loewy, 1981; Taylor and Weaver, 1992; Jansen et al., 1995; McAllen et al., 1995; Campos and McAllen, 1999; Morrison et al., 1999; Huang et al., 2002; Blessing, 2003; Cao and Morrison, 2003; Dampney et al., 2003; Zaretsky et al., 2003a,b; Horiuchi et al., 2004a,b; Nalivaiko et al., 2005). Dashed lines represent unknown and/or indirect projections. Thick line from DMH to RP, and from RP to target organs illustrates a hypothetical descending pathway illustrating the asymmetric functional responses evoked from DMH (see text for details).

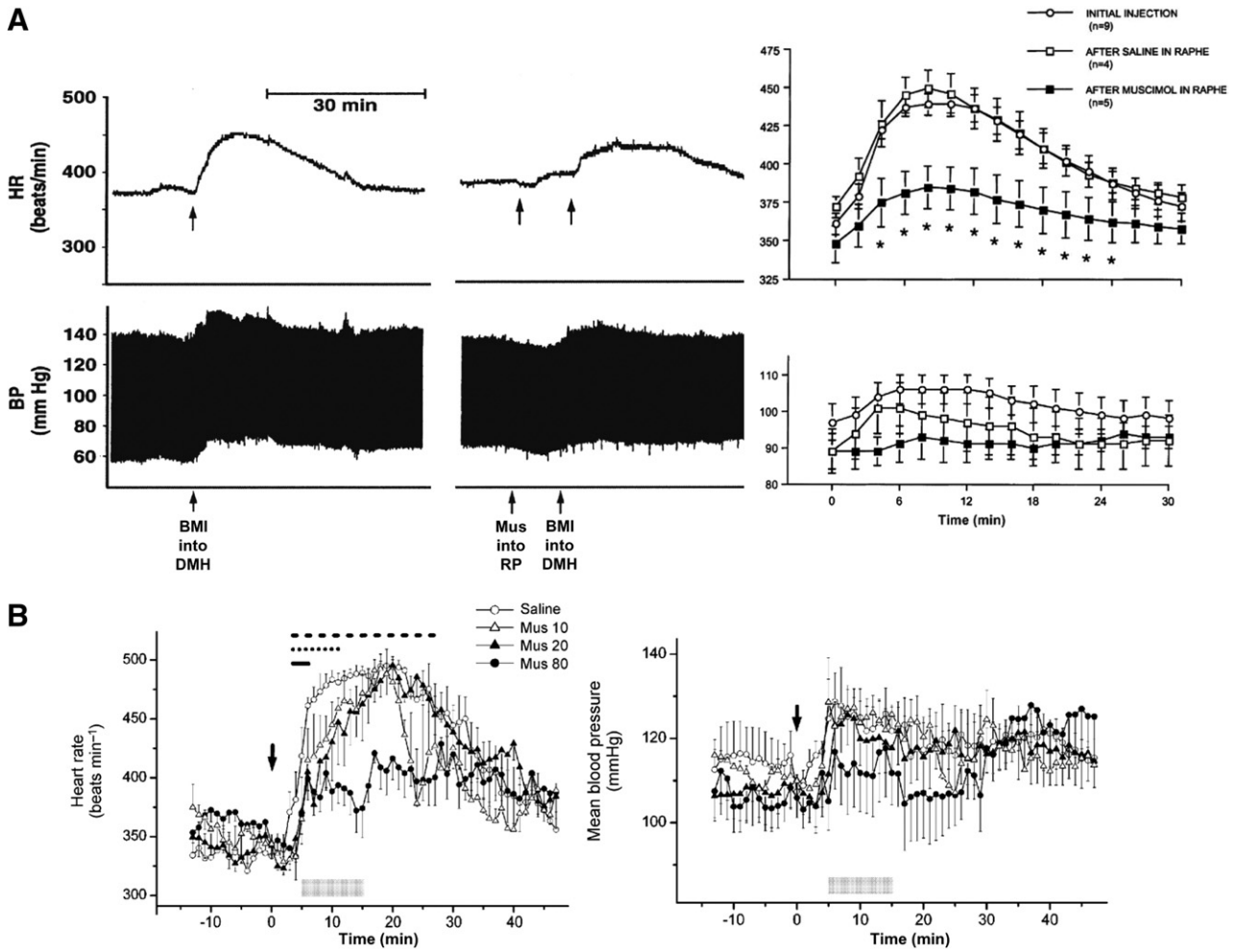

Fig. 3. Raphe neurons are a crucial relay in the pathway responsible for stress-induced tachycardia. (A) Inhibition of raphe neurons, through microinjection of the $GABA_A$ receptor agonist muscimol, reduces the increase in HR, but not in BP, evoked by disinhibition of the DMH (by microinjection of the $GABA_A$ receptor antagonist bicuculline). Left: Example of an original tracing from a representative experiment. Right: Grouped data depicting the changes in HR and BP induced by disinhibition of the DMH after microinjection of muscimol or saline into the RP. * $P<0.05$. (B) Inhibition of raphe neurons, by microinjection of muscimol, reduces the increase in HR, but not in BP, evoked by air-jet stress. Injections were performed a $t=0$ min (arrows), and rats were subjected to air-jet stress during stress trial between $t=+5$ min and $t=+15$ min (shaded bars). Horizontal lines (top) indicate significant differences from corresponding values after treatment with saline: dashes, 80 pmol; dots, 20 pmol; continuous,10 pmol. BMI, bicuculline methiodide; DMH, dorsomedial hypothalamus; Mus, muscimol; RP, raphe pallidus. Data presented at this figure taken from Samuels et al., J Physiol 538:941-946, 2002 (Panel A) and Zaretsky et al., J Physiol 546:243-250, 2003 (Panel B).

diac sympathetic preganglionic neurons (Amendt et al., 1979; Loewy, 1981; Ter Horst et al., 1996). As demonstrated by Samuels and colleagues (2002), the tachycardia evoked by activation of neurons in the DMH with BMI was markedly suppressed after inhibition of neurons in the RPa with muscimol (Fig. 3A). Subsequent experiments in conscious rats demonstrated that inhibition of the RPa virtually abolished the tachycardia evoked by acute stress (Fig. 3B) but failed to influence the tachycardia produced by baroreceptor unloading (Zaretsky et al., 2003b). Further support for the involvement of neurons in the RPa in the tachycardia evoked by stress comes from experiments showing that direct injection of BMI into RPa neurons evokes tachycardia of similar magnitude as that evoked by activation of neurons in the DMH (Samuels et al., 2002; Cao and Morrison, 2003). Interestingly, inhibition of the RPa in conscious rats has no effect on baseline HR (Zaretsky et al., 2003b), but blockade of $GABA_A$ receptors in the RPa produces sustained increases in cardiac sympathetic activity and in HR even after complete suppression of activity in sympathoexcitatory neurons in the RVLM with muscimol (Cao and Morrison, 2003). Therefore, the cardiac sympathoexcitation and tachycardia evoked by activation of neurons in the RPa can occur independently of excitation of sympathetic premotor neurons in the RVLM that normally provide the excitatory drive to support basal cardiac sympathetic activity and HR. As proposed by Cao and Morrison (2003), dorsomedial hypothalamic neurons apparently act to reduce or overcome the tonic inhibition of these RPa neurons, which in turn provide an excitatory drive to spinal cardiac sympathetic

preganglionic neurons to augment cardiac sympathetic activity and HR (Fig. 2, pathway 9).

PERIAQUEDUCTAL GRAY: A SOURCE OF EXCITATORY INPUT TO NEURONS IN THE DMH?

Ultimately, a model that relies on the regulation of neuronal activity through disinhibition must include a mechanism responsible for excitation of the neuronal population being studied (Morrison, 2004). As is seen after acute stress or disinhibition of neurons in the DMH with BMI, a tachycardic response can also be induced by stimulating neurons in the DMH with agonists of EAA receptors (Soltis and DiMicco, 1991a, 1992; Tanaka and McAllen, 2008). The first structure evaluated as a source of excitatory input to DMH neurons was the amygdala, a structure well-known to be involved in stress and anxiety (LeDoux, 2007). Chemical stimulation of the amygdala results in cardiovascular changes that are abolished after blockade of glutamatergic receptors in the DMH (Soltis et al., 1998). However, recent attempts to reveal the descending cardiovascular connections from DMH led us also to consider the periaqueductal gray region (PAG) (da Silva et al., 2003, 2006) (Fig. 2 pathway 6).

Our findings that increases in HR and MAP seen in air jet stress were reduced by microinjection of muscimol into the lateral/dorsolateral region of PAG (l/dlPAG) (de Menezes et al., 2008), in the same manner that the inhibition of DMH neurons alters the cardiovascular response to air jet stress (Stotz-Potter et al., 1996b), suggested that neurons in the l/dlPAG constitute downstream effectors for cardiovascular changes evoked from the DMH. Surprisingly, however, we also observed that microinjection of muscimol into the l/dlPAG reduced the increases in plasma adrenocorticotropic hormone (ACTH) evoked by air jet stress. Increases in plasma ACTH seen in this paradigm represent activation of the hypothalamic-pituitary-adrenal axis, a hallmark of the response to stress, and have been proposed to be mediated in large part through a direct projection from neurons in the DMH to the hypothalamic paraventricular nucleus [PVN; for review, see (DiMicco et al., 2002)]. On the other hand, neurons in the l/dlPAG do not project to the PVN (Cameron et al., 1995).

This hypothesis that the PAG is a source of excitatory input to neurons in the DMH during stress was validated by demonstrating that the increases in HR, BP and core body temperature produced by microinjection of the excitatory amino acid (NMDA) into l/dlPAG in conscious rats were markedly attenuated either by neuronal inhibition (microinjection of muscimol) or by blockade of glutamate transmission (microinjection of NBQX+Ap5) within the DMH, but not within the PVN (de Menezes et al., 2009). Likewise, microinjection of muscimol into the DMH of anaesthetized rats reduced the increases in BP as well as the increases in phrenic and renal sympathetic nerve activity produced by the activation of the dlPAG (Horiuchi et al., 2009).

Taken together, these data demonstrated that the physiological responses produced by activation of the l/dlPAG depend on neuronal activity in the DMH. Thus, the l/dlPAG may represent one of several regions that provide glutamatergic excitation to neurons in the DMH (Fig. 2, pathway 5) whose activation is ultimately responsible for physiological changes seen in experimental stress. Previous data from anatomical studies are consistent with this notion. For instance, it is known that neurons in the l/dlPAG send axonal projections to neurons located in the region of the DMH (Shaikh et al., 1987; Cameron et al., 1995; Siegel et al., 1997). Also, chemical or electrical stimulation of the l/dlPAG increases the expression of c-fos, a marker for neuronal activation (Dragunow and Faull, 1989), in the DMH, where the terminals of projections from the l/dlPAG can also be found (de Oliveira et al., 2000; Borelli et al., 2006). It important to observe that, in the study of de Oliveira, the increase in c-fos expression was restricted to the dorsomedial nucleus and occurred mainly on the side ipsilateral to the stimulation site in the dlPAG. This fact suggests that the increase in c-fos expression within the DMH was due to the specific activation of the neurons in the PAG and not to the generalized behavioral arousal that was also produced. Thus, during stress, afferents from neurons in the l/dlPAG, perhaps along with those from other regions, might act to excite neurons in the DMH. On the other hand, the tonic inhibitory drive that is present under resting conditions might at the same time be withdrawn, thus changing the balance between GABAergic and glutamatergic transmission that occurs in the DMH [see (DiMicco et al., 2002)]. These shifts would then lead to activation of (1) CRH-containing neurons in the PVN to stimulate the secretion of ACTH, and (2) autonomic centers in the brainstem to increase HR, MAP, temperature and respiratory rate. It is important to consider that the projections through which the l/dlPAG influences the DMH do not necessarily have to be direct. For example, the dlPAG has major projections to the cuneiform nucleus and to the superior lateral parabrachial nucleus in the pons (Lisa et al., 1989b; Carrive, 1993; Krout et al., 1998), and these in turn have projections to the hypothalamus, including the DMH (Bester et al., 1997; Lam et al., 1997).

The results of the studies showing that the physiological changes produced by the activation of the l/dlPAG neurons depend on neuronal activity in the DMH (de Menezes et al., 2009; Horiuchi et al., 2009), combined with data from the earlier studies showing that the changes evoked by disinhibition of the DMH are, also, dependent on the activation of l/dlPAG neurons (da Silva et al., 2003, 2006; de Menezes et al., 2006), requires alternative explanations to the hypothesis presented above. In this regard, de Menezes and colleagues (2009) proposed two distinct hypotheses that are consistent with the data concerning the relationship between the DMH and the l/dlPAG. One possibility is that these regions are reciprocally connected to form a functional network involved in the stress response. In this case, the stimulation of either region would facilitate the activation of the neurons in the other region. Another possibility is that this critical facilitation from neurons in the DMH and in the PAG converges on common medullary targets related to the physiological responses

evoked from either region. Once again, loss of either source of background facilitation may effectively weaken responses evoked from the other.

NUCLEUS TRACTUS SOLITARIUS: STRESS, DMH AND BAROREFLEX MODULATION

Acute psychological stress and stimulation of the DMH can both generate physiological and behavioral responses, as described above, with the main cardiovascular effect being increases in HR and BP (Stotz-Potter et al., 1996a,b; Fontes et al., 2001; DiMicco et al., 2002; da Silva et al., 2003; de Menezes et al., 2006). In addition to these changes, it is known that both stress and stimulation of the DMH can modulate the baroreceptor reflex (Kunos and Varga, 1995; Hatton et al., 1997; Schadt and Hasser, 1998; Sevoz-Couche et al., 2003; McDowall et al., 2006). This modulation during the defense reaction is necessary to ensure that the changes in HR and BP can occur simultaneously, without compromise of either response (i.e. increases in HR or BP). Studies in conscious animals indicate that during stress the increases in HR and BP are accompanied by resetting of the baroreceptor reflex (Hatton et al., 1997; Schadt and Hasser, 1998). In these studies, the reflex control of HR was reset to higher levels of arterial pressure without any changes in the gain. In addition, recent evidence by Kanbar and colleagues (2007) demonstrated that the baroreflex control of sympathetic activity is reset and sensitized during emotional stress (Kanbar et al., 2007).

The exact nature of DMH influence in the baroreceptor reflex remains to be determined. An early report by Kunos and Varga showed that ipsilateral intra-nucleus tractus solitarius (NTS) injection of BMI or 2-OH-saclofen ($GABA_B$ antagonist), attenuated the tachycardia elicited by BMI injection into the DMH. The tachycardia was also inhibited by intra-NTS administration of EEA receptor channel blockers. Authors concluded that the descending input from the DMH to the NTS releases GABA via glutamate acting on ionotropic glutamate receptors located on GABAergic interneurons (Kunos and Varga, 1995). This mechanism would inhibit baroreflex bradycardia during activation of DMH. Similarly, a study by Sevoz-Couche and colleagues (2003) demonstrated that electrical stimulation of the DMH in anaesthetized rats also inhibits baroreflex bradycardia. However, a recent report by McDowal and colleagues showed that chemical disinhibition of DMH neurons resets the baroreflex to higher levels of arterial pressure, in the same way stress does (Hatton et al., 1997; Schadt and Hasser, 2001; Kanbar et al., 2007), with the baroreflex remaining effective and without losing sensitivity (McDowall et al., 2006).

BRAIN FUNCTIONAL ASYMMETRY AND DMH

Left-right differences in the functional properties of bilateral nervous system regions are known as lateralization of function. This phenomenon has been observed at different levels of the neuraxis (Toga and Thompson, 2003; Stephan et al., 2007), including the hypothalamus from several species (Harris et al., 1996). Studies revealed that, under some conditions, stress may generate lateralized and imbalanced autonomic outflow (Critchley, 2005). This asymmetric autonomic activity may cause cardiac arrhythmias, (Lane et al., 1992a,b). Wittling et al. found a functional division between the cerebral hemispheres with the left dominant in generating parasympathetic activity to the heart while the right plays a greater role in generating the sympathetic activity to the myocardium (Wittling et al., 1998a,b). If this division is physiological, it may provide a substrate for described cardiac arrhythmias. Pathways from the DMH are predominantly lateralized such that most neurons on one side do not project contralaterally, but rather they are organized as ipsilateral “mirrors” (ter Horst and Luiten, 1986; Thompson et al., 1996). Additionally, anatomic projections from other nuclei involved in autonomic control to sympathetic preganglionic neurons in the intermediolateral column are also lateralized (Amendt et al., 1979; Blessing et al., 1981; Zagon and Smith, 1993).

In the hypothalamus, the hypothesis of functional asymmetry was first reported based upon the observation that electrical stimulation of the right hypothalamus evokes greater tachycardia than that evoked by identical stimulation of the left (Fang and Wang, 1962). Recently, we demonstrated that unilateral disinhibition of neurons in the

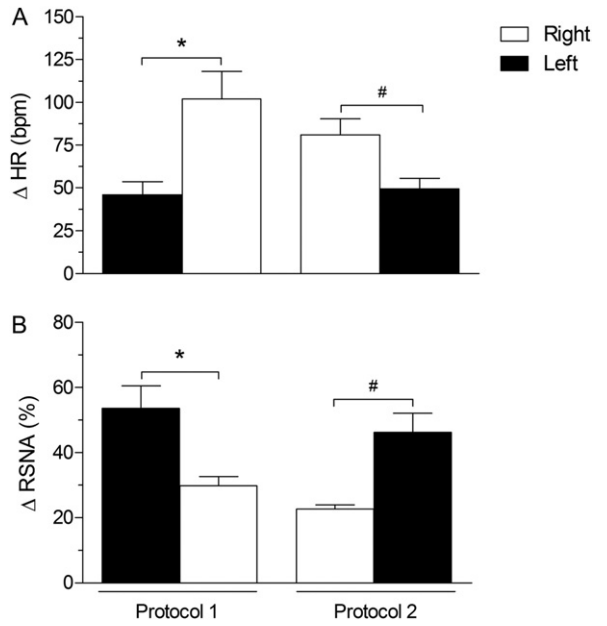

Fig. 4. Maximal changes in cardiovascular parameters from baseline evoked by unilateral microinjection of BMI into right (white bars) and left DMH (black bars) on two experimental protocols. Sequence for injections into unilateral (R or L) DMH followed two different orderliness: Protocol 1—First microinjection was done into L-DMH and the second was into R-DMH; Protocol 2—Sequence for injections was reverse of that used in protocol 1, for example, first into R-DMH and second into L-DMH. (A) Heart rate (HR) and (B) renal sympathetic nerve activity (RSNA) sampled from left renal nerve. * $P<0.05$—protocol 1 (L vs. R); # $P<0.05$—protocol 2 (R vs. L). (A) shows asymmetry with clear predominance of R-DMH in provoking greater positive chronotropy. (B) shows lateralization in the pathways from unilateral DMH which controls ipsilateral RSNA. Data taken from Xavier et al., Neuroscience 164:1360-1368, 2009.

DMH with BMI evokes Fos expression in different nuclei, including the DMH itself, the midline rostral RP, and the lateral septal nucleus, the parvocellular and magnocellular subdivisions of the PVN, the NTS, and the ventrolateral medulla. In the latter bilateral regions, labeling was increased on both sides but was markedly greater ipsilateral to the site of DMH stimulation (Zaretskaia et al., 2008). In determining if cardiac sympathoexcitation evoked by activation of neurons on one side of the DMH is transmitted preferentially through ipsilateral relays, we found that disinhibition of the right DMH evokes a greater tachycardia than that evoked from the left DMH (Xavier et al., 2009) (Fig. 4). Additionally, disinhibition of the right DMH evokes substantially larger changes in cardiac contractility compared to those evoked from left DMH. This effect is independent of the simultaneous changes in heart rate and afterload and so might be interpreted as a direct positive inotropic effect. Interestingly, in the same study we detected a greater number of ectopic beats during the 10 min following injections of BMI into the right DMH (Xavier et al., 2010). This finding prompted us to speculate that recruiting the right DMH during stress exposure might improve the range of cardiac responses and increase the risk of arrhythmic episodes.

The possibility that descending input to the DMH from brain structures, such as the insular cortex, may be asymmetric should also be considered (see Fig. 2). First, there is anatomical and functional evidence for connections between the insular cortex and the hypothalamus (Cechetto and Chen, 1990). Second, neural activity in the insular cortex may have an arrythmogenic role according to past findings. In rats, the cardiac effects of stimulation of the insular cortex mimic the repolarization and structural changes that occur with catecholamine-induced cardiomyopathy seen under certain clinical circumstances, including death following extreme and prolonged stress, and these effects are likely associated with sympathetic neural activation of the ventricular myocardium (Oppenheimer, 2007). Similarly, in humans, insular damage may produce effects on cardiac repolarization (Sander and Klingelhofer, 1994). Third, there is evidence suggesting lateralization and specialization of cardioregulatory function within the insular cortex. The right insular cortex has been primarily implicated with modulation of cardiac sympathetic nerve activity and the left with effects primarily on cardiac vagal activity. Interestingly, patients with stroke lateralized to the left insular cortex reportedly exhibit impaired sympathovagal balance, with one third of the stroke patients developing sinus tachycardia even in the absence of significant coronary disease (Oppenheimer, 2007). Whether or not insular cortical imbalance might result in consequent asymmetric activity of DMH neurons for triggering adverse cardiac outcomes remains to be determined.

CONCLUSION AND PERSPECTIVES

In conclusion, although many of the details regarding the role of the dorsomedial hypothalamus in the cardiovascular response to emotional stress remain to be determined, considerable progress has been made in the past few years in determining the central pathways involved. Undoubtedly, a critical step is to further investigate the implications of the lateralization observed in the descending pathways from the DMH. The role of the DMH in adverse cardiac events observed after cortical stimulation or damage deserves extensive investigation. Elucidating the functional organization of this network could provide a framework for understanding how, in some conditions, stress results in autonomic imbalance resulting in cardiovascular risk.

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