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SUPRAMEDULLARY MODULATION OF SYMPATHETIC VASOMOTOR FUNCTION

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SUMMARY

1. Supramedullary structures including the ventral medial prefrontal cortex (MPFC) and the midbrain cuneiform nucleus (CnF) project directly and indirectly to premotor sympathoexcitatory neurons of the rostral ventrolateral medulla (RVLM) that are critically involved in the generation of sympathetic vasomotor tone.

2. Electrophysiological studies have demonstrated that activation of depressor sites within the MPFC is associated with splanchnic sympathetic vasomotor inhibition and inhibition of the activity of RVLM sympathoexcitatory neurons.

3. Antidromic mapping and anatomical studies support the notion that a relay in the nucleus tractus solitarius is involved in the cardiovascular response to MPFC stimulation.

4. The midbrain CnF, which lies adjacent to the midbrain periaqueductal grey, is a sympathoexcitatory region of the midbrain reticular formation. Sympathoexcitatory responses evoked from the CnF are associated with short-latency excitation of RVLM neurons.

5. Cuneiform nucleus stimulation induces the expression of mRNA for the immediate early genes c-*fos* and *NGFI-A* in midbrain, pontine and hypothalamic structures.

6. The MPFC and CnF are supramedullary structures with opposing modulatory influences on sympathetic vasomotor drive, whose roles in cardiovascular control mechanisms warrant further investigation.

Key words: blood pressure, cardiovascular system, rostral ventrolateral medulla, sympathetic vasomotor outflow.

INTRODUCTION

In recent years the focus of central cardiovascular control research has been on the origins of sympathetic vasomotor tone and the neurocircuitry associated with reflex circulatory control.[1–4] The importance of spinally projecting neurons within the rostral ventrolateral medulla (RVLM) in the generation of sympathetic vasomotor tone has been established in a number of species,[3,5–7] so that these neurons are generally regarded as premotor sympathoexcitatory neurons that provide tonic drive to the sympathetic preganglionic vasomotor neurons in the thoracolumbar regions of the spinal cord. In addition, an increasing body of evidence suggests that the central nervous system is capable of generating highly differentiated patterns of sympathetic vasomotor activity resulting in regionally specific changes in blood flow,[8,9] rather than a global activation of the sympathetic nervous system, as first postulated by Cannon.[10] Differentiated patterns of regional sympathetic vasomotor outflow are probably expressed through activation of specific subgroups of RVLM sympathoexcitatory neurons committed to specific groups of sympathetic preganglionic neurons which innervate appropriate peripheral vascular beds. It is unlikely that the RVLM itself integrates the specific sensory inputs that lead to selected patterns of regional sympathetic response; this is likely to be the role of higher brain structures that have access to sensory information relevant to the behavioural state of the organism. For example, it has been repeatedly demonstrated that electrical and chemical stimulation of regions within the midbrain periaqueductal grey area (PAG) or the hypothalamus leads to a differential sympathetic vasomotor response and pattern of regional vascular response.[11–17] Presumably, neurons in the PAG and hypothalamus are capable of activating specific subgroups of RVLM sympathoexcitatory neurons by virtue of direct connections with the RVLM.[16,18–20]

SUPRAMEDULLARY STRUCTURES THAT INFLUENCE SYMPATHETIC VASOMOTOR TONE

There are a number of supramedullary regions other than the PAG and hypothalamus that are capable of influencing circulatory function (for a recent review see Dampney[2]). In the present review we will focus on two supramedullary structures that are known to have opposing influences on arterial blood pressure (BP) and sympathetic vasomotor activity: the depressor area of the medial prefrontal cortex (MPFC) and the cuneiform nucleus (CnF), a sympathoexcitatory area of the lateral midbrain reticular formation (Fig. 1).

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MEDIAL PREFRONTAL CORTEX: A CORTICAL SYMPATHOINHIBITORY REGION

The medial prefrontal cortex (MPFC; Fig. 1) has been defined as the cortical region that receives afferent input from the mediodorsal thalamic nucleus (MD)[21,22] and is subdivided into the prelimbic (PL) and infralimbic (IL) areas. The PL area receives afferents predominantly from the medial and lateral MD,[23] while the IL area does not appear to be a target of these projections.[22] The MPFC and MD are connected reciprocally[21,24–26] and the input to the MPFC from the MD is probably glutamatergic.[27]

The MPFC has been termed a 'visceromotor' cortical area.[28,29] Whether the MPFC has any special claim to this terminology is uncertain as a number of other, albeit linked, cortical regions also influence visceral motor function. Nevertheless, the MPFC contains neurons that project to a number of other brain regions associated with visceral motor control or visceral afferent processing and its activation leads to various changes in the activity of effector organs and tissues influenced by the autonomic nervous system.[28] Thus, electrical stimulation of this region elicits changes in arterial BP,[30–32] heart rate, respiration, gastric motility[28,33] and potentially micturition, as the MPFC projects to Barrington's nucleus, the pontine micturition centre.[34] Electrical stimulation of the MPFC usually elicits depressor responses in the anaesthetized rat, although pressor responses have been reported when the MPFC is stimulated in awake animals.[30] Cechetto and Saper[35] reviewed the literature on the role of the MPFC in cardiovascular control and since then we and other researchers have sought additional evidence for such a role and for the mechanisms associated with MPFC stimulation-evoked depressor responses.

PATHWAYS OF THE CORTICAL SYMPATHOINHIBITORY SYSTEM

The pathway(s) that mediate the depressor response elicited by MPFC stimulation have not been completely elucidated. A potential candidate pathway was identified when a number of tract-tracing studies identified direct projections from the MPFC to brainstem structures associated with autonomic function.[36–38] Neuroanatomical studies performed in rats, rabbits and cats have demonstrated that the nucleus tractus solitarius (NTS) in the dorsomedial medulla receives afferents not only from peripheral visceral sources, but also from supramedullary structures, including the MPFC and the insular cortex (IC)[29,36–45] (Fig. 1). These observations led to speculation that the cardiovascular (and/or other autonomic) responses evoked by microstimulation of the MPFC may be mediated by a projection to the NTS. As yet, there is no unequivocal evidence that cortical neurons projecting to the NTS actually synapse with NTS neurons involved in cardiovascular control. Nevertheless, there is considerable overlap between the sites within the NTS that receive both cortical and cardiopulmonary visceral afferents,[36,46] suggesting that cortical neurons projecting to the NTS may modulate visceral reflex function.

Extracellular single-unit recordings made from the depressor area of the MPFC have demonstrated that neurons in this area may be activated antidromically by stimulation within the depressor area of the NTS.[47,48] Using antidromic mapping techniques,[49] our laboratory has demonstrated that axons of MPFC neurons terminate within a depressor area of the caudal/intermediate NTS.[48] These observations raise the possibility that cortical inputs to the NTS may be involved

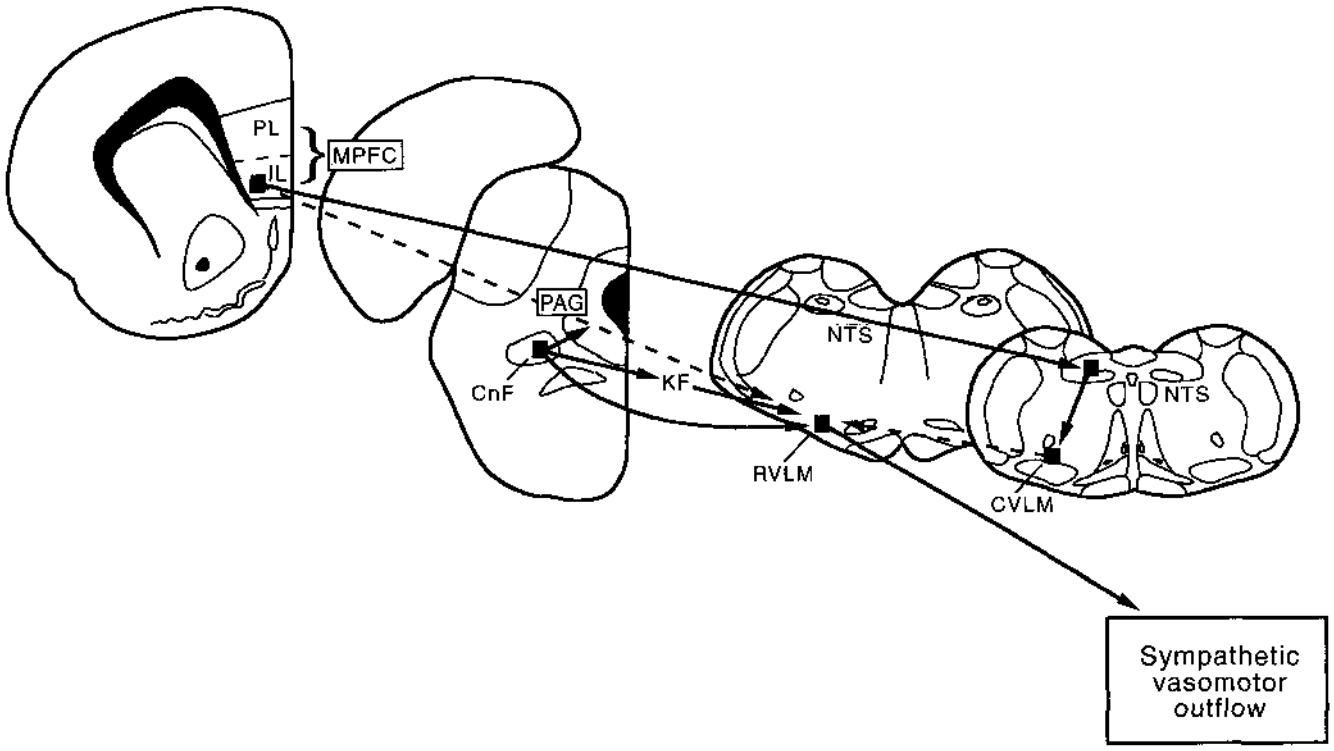

Fig. 1. Anatomical location and projections of the medial prefrontal cortex (MPFC) and midbrain cuneiform nucleus (CnF) to pontomedullary structures associated with central cardiovascular control mechanisms. CVLM, caudal ventrolateral medulla; IL, infralimbic area; KF, Kölliker-Fuse nucleus; NTS, nucleus tractus solitarius; PAG, periaqueductal grey area; PL, prelimbic area; RVLM, rostral ventrolateral medulla. Solid lines represent excitatory pathways; dashed lines represent inhibitory pathways.

in modulation of the baroreceptor reflex. Indeed, it has been demonstrated that excitotoxic lesions of the MPFC reduce the gain of the heart rate baroreflex in normotensive but not in spontaneously hypertensive rats.[28,50,51]

Electrical stimulation of the IL depressor area results in the appearance of Fos-like immunoreactivity in neurons in a number of brain regions known to receive IL afferents, including the NTS and the caudal ventrolateral medulla at the level of the obex (D Owens *et al.*, unpubl. obs., 1996). This suggests that the projection to the NTS is excitatory and is consistent with activation of baroreceptor-related NTS neurons and the production of a depressor response through activation of the baroreflex arc (Fig. 2).[52] It is interesting to note that IC afferents to the NTS are probably also excitatory.[53]

Alternatively, a recent preliminary report indicates that at least part of the MPFC stimulation-evoked depressor response is associated with a relay in the lateral hypothalamic area.[54] Similarly, it has been suggested that neurons within the lateral hypothalamic area participate in the depressor response elicited from the lateral prefrontal cortex, the rostral extension of the IC.[55,56] It is therefore conceivable that the MPFC stimulation-evoked depressor response is mediated by a number of separate pathways that include both hypothalamic as well as medullary relays (Fig. 2).

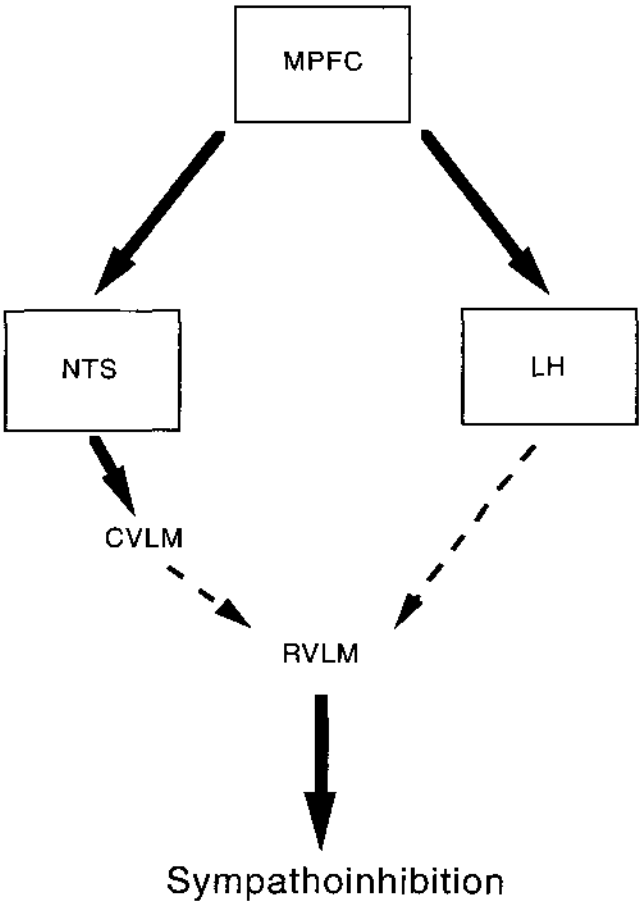

Fig. 2. Potential pathways mediating medial prefrontal cortex (MPFC) stimulation-evoked depressor and sympathoinhibitory responses. CVLM, caudal ventrolateral medulla; LH, lateral hypothalamic area; NTS, nucleus tractus solitarius; RVLM, rostral ventrolateral medulla. Solid lines represent excitatory pathways; dashed lines represent inhibitory pathways.

In a recent study, our laboratory examined the influence of stimulation of the MPFC depressor region on BP, sympathetic vasomotor discharge and the discharge of the premotor sympathoexcitatory neurons of the RVLM.[57] It was demonstrated that depressor responses elicited from the MPFC are associated with inhibition of the sympathetic vasomotor outflow, particularly to the abdominal visceral vasculature innervated by the splanchnic nerve.[57] These depressor and sympathoinhibitory responses were elicited from a wide range of dorsoventral locations within the MPFC. This is possibly due to the fact that MPFC neurons projecting to structures such as the NTS are located in both the PL and IL areas, although they are found predominantly in the latter.[28] Electrical stimulation of the MPFC also resulted in the inhibition of some RVLM sympathoexcitatory neurons.[57] These neurons are profoundly barosensitive and are considered to be critical in the generation of sympathetic vasomotor tone.[3,58] This suggests that MPFC stimulation-evoked depressor and sympathoinhibitory responses are mediated, at least in part, by inhibition of RVLM premotor, sympathoexcitatory neurons. Although a direct projection from the MPFC to the area of the RVLM containing premotor sympathoexcitatory neurons has been reported previously,[42,59] this projection appears to be relatively sparse and, therefore, may not have a major role in mediating cortically evoked depressor responses. Alternatively, activation of the MPFC probably results in inhibition of the activity of RVLM neurons via a polysynaptic route that may include relays in the NTS and/or the hypothalamus.

In summary, the MPFC contains a depressor and sympathoinhibitory region whose role in central cardiovascular control mechanisms remains obscure. However, it is probable that the MPFC is involved in the mechanisms that lead to coordination of circulatory function with ongoing behaviour.

CUNEIFORM NUCLEUS: A MIDBRAIN PRESSOR AND SYMPATHOEXCITATORY REGION

The cuneiform nucleus is situated lateral to the midbrain trigeminal nucleus adjacent to the caudal lateral PAG area.[60] Anatomical investigations have demonstrated a projection from the CnF to a number of structures that are associated with cardiorespiratory mechanisms.[60] Furthermore, a projection from CnF to the raphe magnus nucleus, an area involved in a descending pain inhibitory system, has also been described previously.[60–62] The CnF projects to the PAG and some of these neurons may be glutamatergic.[63,64] These connections suggest that the CnF may be involved in some way with the central circuits associated with endogenous pain control systems.[65]

The PAG has also been implicated in central circulatory control,[60] where it is considered to be critical for the expression of the autonomic and behavioural components of the defence response.[16,20] Similarly, it has been suggested that the CnF could be involved in a form of defensive behavioural and cardiovascular response to threatening or painful stimuli.[66] Chemical and electrical stimulation of the superior colliculus also results in cardiovascular responses similar to CnF stimulation[67] and it has been speculated that, as the superior colliculus receives largely visual input, a pathway involving the superior colliculus, the CnF and other, as yet unidentified structures, may be involved in mediating defence responses associated with threatening visual stimuli.[67]

PATHWAYS OF THE CnF SYMPATHOEXCITATORY SYSTEM

It is conceivable that activation of the CnF may excite neurons in the PAG which, in turn, project to the premotor, sympathoexcitatory neurons of the RVLM.[16,20,59] A direct projection from the CnF to the sympathoexcitatory area of the RVLM has been reported[60] but appears to be relatively sparse. While this does not necessarily preclude its involvement in the cardiovascular responses elicited from the CnF, earlier retrograde tracing studies from the RVLM have not reported a similar projection.[59]

It has also been postulated that the cardiovascular responses elicited from the CnF may be mediated by its much stronger connections with the Kölliker-Fuse nucleus, which projects strongly to the RVLM.[60] Electrical stimulation of both of these areas leads to elevation of arterial BP.[60,68,69] Our laboratory has examined the mechanism of the sympathoexcitatory response elicited by electrical stimulation of the CnF using: (i) electrophysiological techniques, such as extracellular single unit recording; and (ii) molecular biological techniques, such as *in situ* hybridization histochemical detection of immediate early gene (IEG) mRNA as an index of neuronal activation.[70] Electrical stimulation of the CnF elicited a pressor response accompanied by excitation of the lumbar sympathetic vasomotor discharge and activation of RVLM sympathoexcitatory vasomotor neurons.[71] The peak latency for excitation of RVLM sympathoexcitatory neurons by CnF stimulation (16 ± 1 ms) approximates the difference between the earliest peak latency of the lumbar sympathoexcitatory response elicited by CnF stimulation (102 ± 3 ms) and the peak latency of the lumbar sympathoexcitatory response elicited by RVLM stimulation (81 ± 1 ms; Fig. 3b).[16] These observations are consistent with the hypothesis that the RVLM relays CnF stimulation-evoked sympathoexcitatory responses.

Rostral ventrolateral medulla premotor sympathoexcitatory neurons have been subdivided into two major groups based on conduction velocity of the spinally projecting axon and sensitivity to catecholamines.[3,72] Electrical stimulation of the RVLM elicits a bimodal sympathoexcitatory response (two peaks of sympathoexcitation with different latencies), probably as a result of activation of the medullospinal neurons with different conduction velocities.[73] Interestingly, stimulation of the CnF produced a bimodal sympathoexcitatory response with latencies that are compatible with activation of the RVLM premotor sympathoexcitatory neurons with different axonal spinal conduction velocities.[71,74] An additional or alternative explanation for the late peak of sympathoexcitation may also be that CnF stimulation excites slow-conducting cells within the raphe pallidus nucleus, which may have a sympathoexcitatory function.[75]

Neuroanatomical studies indicate that the CnF projects only weakly to the RVLM.[59,60] This suggests that the pathway from the CnF mediating sympathoexcitation may be polysynaptic and involves a relay located elsewhere (Fig. 3). A potential candidate may be the Kölliker-Fuse nucleus of the dorsolateral pons, which receives afferents from the CnF.[60] Studies that have examined the IEG response to CnF stimulation have supported this notion.[76,77] Cuneiform nucleus stimulation produced significant increases in the levels of

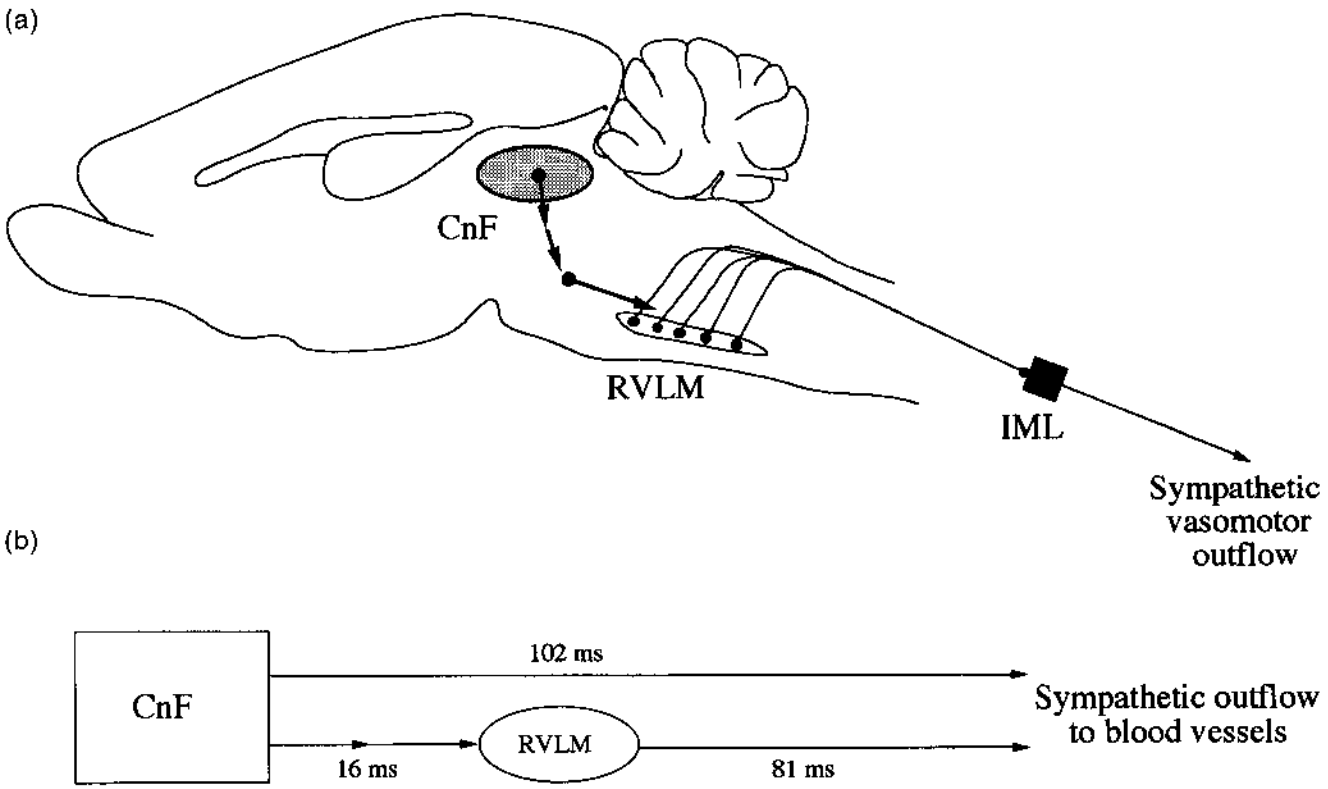

Fig. 3. (a) Cuneiform nucleus (CnF) sympathoexcitatory pathway. Activation of the CnF produces activation of the sympathetic vasomotor outflow by activation of premotor, sympathoexcitatory neurons of the rostral ventrolateral medulla (RVLM). This is most probably a polysynaptic input to the RVLM. (b) Electrical stimulation of the CnF activates RVLM sympathoexcitatory neurons (latency = 16 ms) and sympathetic vasomotor outflow (latency = 102 ms). See text for discussion.

IEG mRNA (c-*fos* and *NGFI-A*, nerve growth factor inducible form, type A) in the Kölliker-Fuse nucleus and parabrachial complex ipsilaterally and the dorsal PAG area bilaterally. In addition, various forebrain structures, such as the ventromedial, dorsomedial and lateroanterior hypothalamic nuclei and lateral and anterior hypothalamic areas, displayed significantly elevated levels of IEG mRNA.[76]

At present, the role of the CnF in central cardiovascular control is uncertain. The limited evidence available suggests that the CnF may be involved in the autonomic and behavioural components of defensive responses to painful or threatening stimuli.[66]

In summary, stimulation of the CnF produces elevations of arterial BP and sympathetic vasomotor activity, at least in part, by activating RVLM sympathoexcitatory vasomotor neurons. Furthermore, the CnF appears to be an additional supramedullary site from which sympathetic vasomotor responses may be elicited but whose precise role in central cardiovascular control remains to be elucidated.

POTENTIAL FUNCTIONAL ROLES OF THE MPFC AND CnF IN CENTRAL CARDIOVASCULAR CONTROL MECHANISMS

Supramedullary structures with anatomical connections to structures known to be involved in central cardiovascular control mechanisms are firmly established and are probably important for the generation of patterns of circulatory response and adjustment in concert with behavioural change. It has been suggested previously that the MPFC may be involved in the termination of defensive behaviour[78] or in the development of habituation to stimuli, which induce defence-like responses. The involvement of the CnF in nociceptive mechanisms[79] suggests that it may be implicated in the cardiovascular responses to painful or threatening stimuli.[66] In addition, the CnF appears to coincide with the so-called midbrain locomotor region, which is active during exercise[80] and so may participate in the cardiovascular response observed during physical activity.

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