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Inhibitory modulation of the cardiovascular defence response by the ventrolateral periaqueductal grey matter in rats

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Summary. In rats anaesthetised with alphaxalone/alphadolone, electrical stimulation in the dorsal periaqueductal grey matter (PAG) evoked a pressor response with tachycardia, vasodilatation in the hindlimb and hyperpnoea: a pattern of response known as the defence reaction. Microinjection of the synaptic excitant, D,L-homocysteic acid (DLH), but not saline, into the ventrolateral PAG at the level of the decussation of the superior cerebellar peduncle (approximately 7.3–8.3 mm caudal to bregma) produced a reduction in the size of the cardiovascular components of the defence reaction evoked by electrical stimulation in the dorsal PAG. Injections of DLH made outside this region had no effect on the defence response. Injection of DLH into the "defence inhibition area" had no effect on the pressor response evoked distally in the efferent pathway for the defence reaction, by electrical stimulation in the rostral ventrolateral medulla (RVLM). Activation of neurones in a restricted portion of the caudal ventrolateral PAG appears to modulate activity in the descending pathway for the defence response evoked from the dorsal PAG. It is argued that the inhibitory interaction probably occurs at the level of synapses in the RVLM.

Key words: Defence response – Ventrolateral periaqueductal grey matter – Rostral ventrolateral medulla – Rat

Introduction

Stimulation in the dorsal and lateral parts of the caudal periaqueductal grey matter (PAG) in anaesthetised or decerebrate animals produces a distinctive pattern of cardiovascular and autonomic adjustments. These include an increase in blood pressure, tachycardia and redistribution of the raised cardiac output to skeletal muscle at the expense of circulation to the skin and viscera. There is also an increase in the rate and depth of respiration, pupillodilatation, exophthalmus and piloerection (Yardley and Hilton 1986; Hilton and Redfern 1986; Carrive et al. 1987). This pattern of cardiovascular response, which has been termed the "defence reaction" (Abrahams et al. 1960) has been shown to accompany fighting behaviour in the freely moving cat (Mancia et al. 1974). It has been suggested that the diversion of cardiac output to skeletal muscle at the expense of the visceral and cutaneous circulation may be a preparatory adjustment to support the increased metabolic demands of skeletal muscle as the animal engages in defensive "fight or flight" behaviour (Hilton 1982; Bandler et al. 1991).

Studies in the anaesthetised rabbit have shown that the cardiovascular components of the defence response evoked by midbrain stimulation can be attenuated following low frequency stimulation of small diameter afferent fibres in a muscle nerve (Huangfu and Li 1985). Huangfu and Li (1987) suggested that the modulatory effects evoked by this type of peripheral nerve input are mediated through an inhibitory pathway which engages neurones in the ventral part of the PAG. The present study was therefore carried out to examine the effects of selective activation of neurones in the ventral PAG on the cardiovascular defence response evoked by stimulating in the dorsal part of the nucleus.

A report of part of this work has been published in abstract form (Lovick 1990).

Methods

Experiments were carried out on 22 rats of either sex, 300–350 g body weight. Following induction with halothane, they were anaesthetised by continuous intravenous infusion of alphaxalone/alphadolone (Saffan, 9–12 mg/kg/h). Blood pressure was measured in a

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carotid artery and the heart rate derived from the pulse waveform. An electromagnetic flow transducer (Carolina Medical Electronics) was used to measure flow in a femoral artery. Vascular conductance was computed off-line by dividing mean flow by mean arterial pressure. The trachea was cannulated and a laboratory-built miniature pneumotachograph fitted to the tracheal cannula to monitor tracheal air flow. Rectal temperature was maintained at 36–37°C by means of a homeothermic blanket. A dorsal craniotomy was performed and the dura incised.

In 16 rats a stainless steel monopolar stimulating electrode was inserted into the dorsal PAG at an angle of 9° to the vertical with the tip pointing caudally, (Fig. 1). The skull was oriented in the attitude described by Paxinos and Watson (1982), i.e. bregma-lambda horizontal. The electrode was positioned at a site where electrical stimulation (10 s trains of 0.5 or 1.0 ms cathodal pulses at 80 Hz, 30–70 μA) produced the characteristic pattern of the defence response i.e. an increase in mean arterial pressure, tachycardia, vasodilatation in the hindlimb, as shown by an increase in both femoral arterial blood flow and vascular conductance, and an increase in the rate and/or depth of respiration (Fig. 4). Stereotaxic coordinates were P6.3–8.3 L0.1–1.0 and H4–5. In a further 6 rats the metal stimulating electrode was positioned in the rostral ventrolateral medulla (RVLM) 10.5–11.5 mm caudal to bregma, 1.25–1.5 mm lateral to the midline and 8.5–9.0 mm below the dorsal surface of the cerebellum. Stimulus parameters were similar to those used in the dorsal PAG. Once the metal stimulating electrode had been correctly positioned a glass micropipette, tip diameter 45–75 μm was inserted vertically into the ventral part of PAG (Fig. 1). The pipette was attached to a 1 μl microsyringe and the assembly filled with either 0.2 M D,L-homocysteic acid (DLH), pH 7.5 or 165 mM NaCl, pH 7.5. Pontamine Sky Blue dye (0.5%) was added to the solutions so that injection sites could be identified in histological material.

Electrical stimulation of the dorsal PAG or RVLM was repeated at intervals of 10 min. The stability of the cardiovascular response was established during a control period of at least 20 min. Then, 1–2 min prior to the next stimulus train, 0.3–0.5 μl of DLH was injected into the midbrain over a period of 10–30 s. The response to the electrical stimulus was monitored at 10 min intervals for a further 20–30 min. Usually, no more than two microinjections were made in any experiment. At the end of each experiment the site of electrical stimulation was marked by depositing iron from the electrode tip with anodal current (20 μA for 10–15 s). The brain was removed for fixation in 1% potassium ferrocyanide in 10% formol saline to develop a Prussian Blue spot. Prior to immersion in the fixative, the cerebellum was dissected away so that the aqueduct could be examined for traces of blue dye which might indicate leakage of the DLH solution into the aqueduct. In all but one case (see Fig. 3, P8.8) there was no sign of dye. After fixation, frozen sections of tissue, 60 μm thick were stained with Neutral Red and stimulating sites and injection sites were identified from the positions of Prussian Blue spots and Pontamine Blue dye marks found in the tissue.

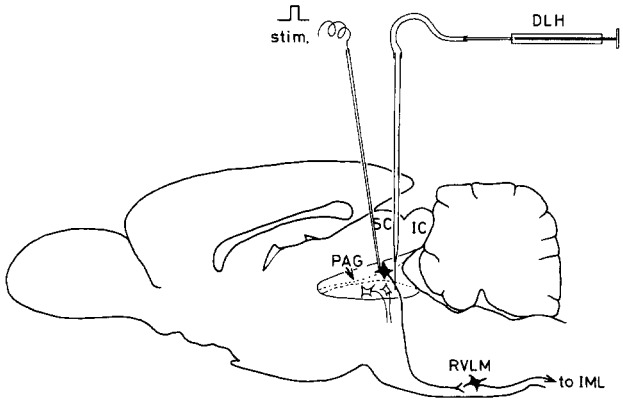

Fig. 1. Schematic drawing of a parasaggittal section through the rat brain to illustrate the arrangement for electrical and chemical stimulation in the PAG. In some experiments the efferent pathway from the dorsal PAG was stimulated electrically at the level of the rostral ventrolateral medulla. Abbreviations: IC: inferior colliculus; IML: intermediolateral cell column; PAG: periaqueductal grey matter; RVLM: rostral ventrolateral medulla; SC: superior colliculus. Broken line in the PAG indicates the level of the aqueduct

Results

Cardiovascular changes evoked by injection of DLH into the PAG

Microinjections of DLH were made at 26 sites throughout the PAG and the sub-adjacent tegmentum. 20 of the microinjections were targetted at the ventrolateral PAG. In addition, a further three injections were made into the dorsolateral PAG and three into the dorsal raphe nucleus. Depending on the precise location of the pipette, microinjection of DLH produced either an increase ($n=6$) or a decrease ($n=20$) in resting blood pressure. At depressor sites, mean arterial pressure was reduced by 3–45 mmHg, mean 24.05 mm Hg and the heart rate fell by 15–95 beats/min, mean 47.7 beats/min (Fig. 2A). The onset of the depressor effect could be seen within 5–80 s, mean 31.5 s of the start of the injection of DLH and lasted for 3–38, mean 15.0 min. This response was always accompanied by vasodilatation in the hindlimb. Hindlimb blood flow increased so that vascular conductance was raised by 6–265%, mean 100.75% above the control level (Fig. 2A). During the early phase of the cardiovascular response there was a brief increase in the depth and, to a lesser extent, in the rate of respiration. The initial hyperpnoea lasted for only 30–120 s. Depressor responses were evoked by injections of DLH made ventral to the level of the aqueduct and 0.5–1.0 mm lateral to the midline (Fig. 3). There did not appear to be any viscerotopic organisation within the depressor area with respect to the size of the various components of the response.

Pressor responses were evoked by injections of DLH into two separate areas: one in the dorsolateral PAG (Fig. 3, 3 sites) and the other medial to the depressor area and ventral to the aqueduct in the region of the dorsal raphe nucleus (Fig. 3, 3 sites). Injection of DLH into the dorsolateral PAG produced an increase in mean arterial pressure of 14–49 mm Hg, mean 30.3 mm Hg whilst injections into the dorsal raphe evoked a rise of 9–71 mm Hg, mean 31.0 mm Hg. A similar pattern of cardiovascular change accompanied the pressor responses evoked from these two areas. Heart rate increased by 10–35 beats/min, mean 20 beats/min (dorsolateral PAG) and by 40–50 beats/min, mean 46.7 beats/min (dorsal raphe). There was also an increase in hindlimb blood flow such that hindlimb conductance was increased by 79–517%, mean 259% after injections into the dorsolateral PAG and by 82–128%, mean 105% by injections into the dorsal raphe nucleus (Fig. 2B and 2C). These patterns of cardiovascular change are similar to those previously described in response to stimulation in the dorsal raphe and dorsal PAG (Piper and Goadsby 1985; Hilton and Redfern 1986). In the present

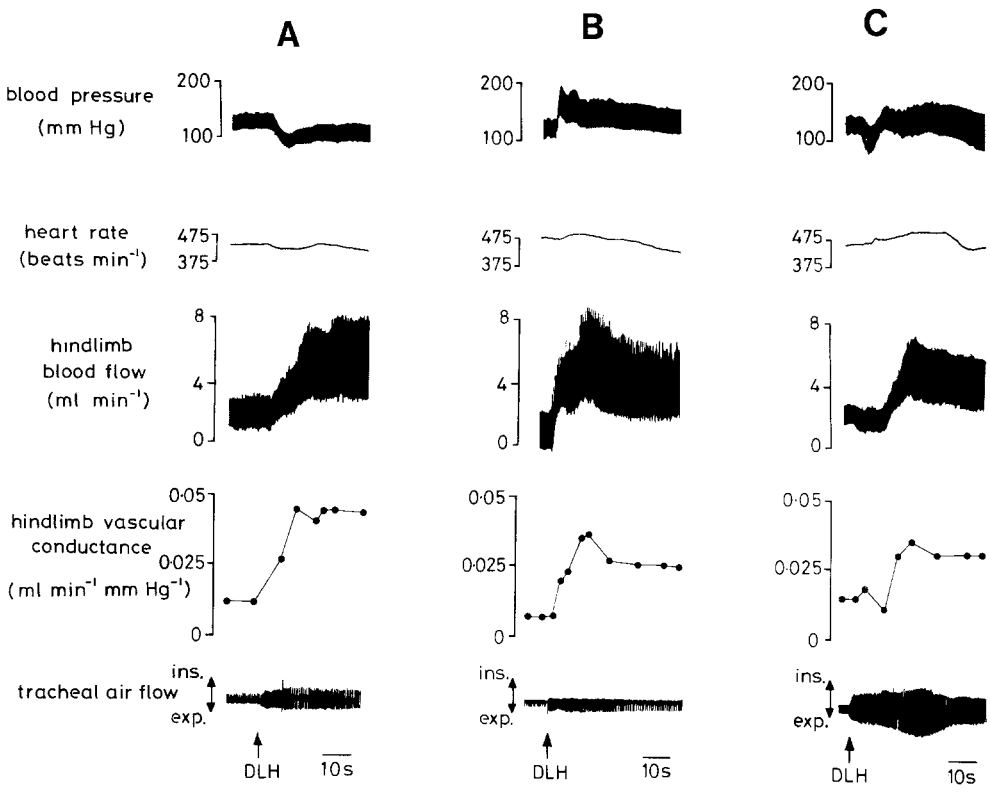

Fig. 2A–C. Examples of 3 different patterns of cardiovascular response evoked by microinjection of DLH into the midbrain. **A** Stimulation in the ventrolateral PAG; **B** stimulation in the dorsolateral PAG; **C** stimulation in the dorsal raphe nucleus

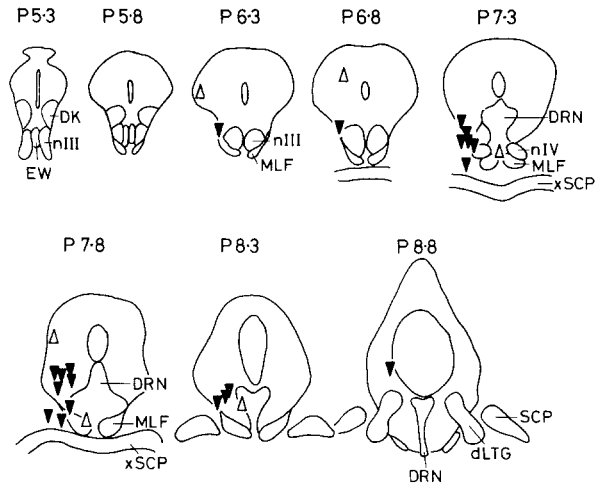

Fig. 3. Drawings of sections through the PAG at different levels to indicate the localisation of injections of DLH. Filled downward-pointing triangles indicate centre of injections which evoked depressor responses; open upright triangles indicate injections which evoked pressor responses. Outline drawings taken from the atlas of Paxinos and Watson (1982). Numbers beneath sections indicate distance in mm caudal to bregma. Abbreviations: DK: nucleus Darkschewitsch; DRN: dorsal raphe nucleus; EW: Edinger-Westfal nucleus; dLTG: dorsal lateral tegmental nucleus; MLF: medial longitudinal fasiculus; SCP: superior cerebellar peduncle; xSCP: decussation of the superior cerebellar peduncle; nIII: oculomotor nucleus; nIV: trochlear nucleus

study the cardiovascular response to stimulation in the dorsolateral PAG was accompanied by an increase in both the rate and depth of respiration (Fig. 2B). Stimulation in the dorsal raphe also evoked an increase in the depth of respiration but there was either no change or only a slight decrease in the rate (Fig. 2C).

Effect of injection of DLH into the PAG on the cardiovascular defence response

The effects of injection of DLH into the PAG on the cardiovascular defence response evoked by electrical stimulation in the dorsolateral PAG was tested at 20 sites. At 6 sites injection of DLH into the ventral PAG significantly attenuated all the cardiovascular components of the defence response. Figure 4 shows sample records taken from one of these experiments. In this example both the pressor response and hindlimb vasodilatation were reduced to about 50% of the control value within 1.5 min of the injection of DLH into the ventrolateral PAG. At this time the tachycardia was abolished and replaced by a bradycardia. Each component of the defence response had returned to control levels within 20 min of the injection of DLH. Figure 5 shows pooled data for the time course of the depression of each of the cardiovascular components of the defence response produced by injection of DLH at the 6 effective sites within the ventrolateral PAG. The whole response was significantly reduced within 1–2 min of injecting DLH and the pressor component and tachycardia remained attenuated for up to 20 min. However the inhibition of the hindlimb vasodilator component was shorter lasting and had returned to control level within 10 min.

The 6 effective stimulation sites were clustered in the ventrolateral PAG and subadjacent tegmentum at the

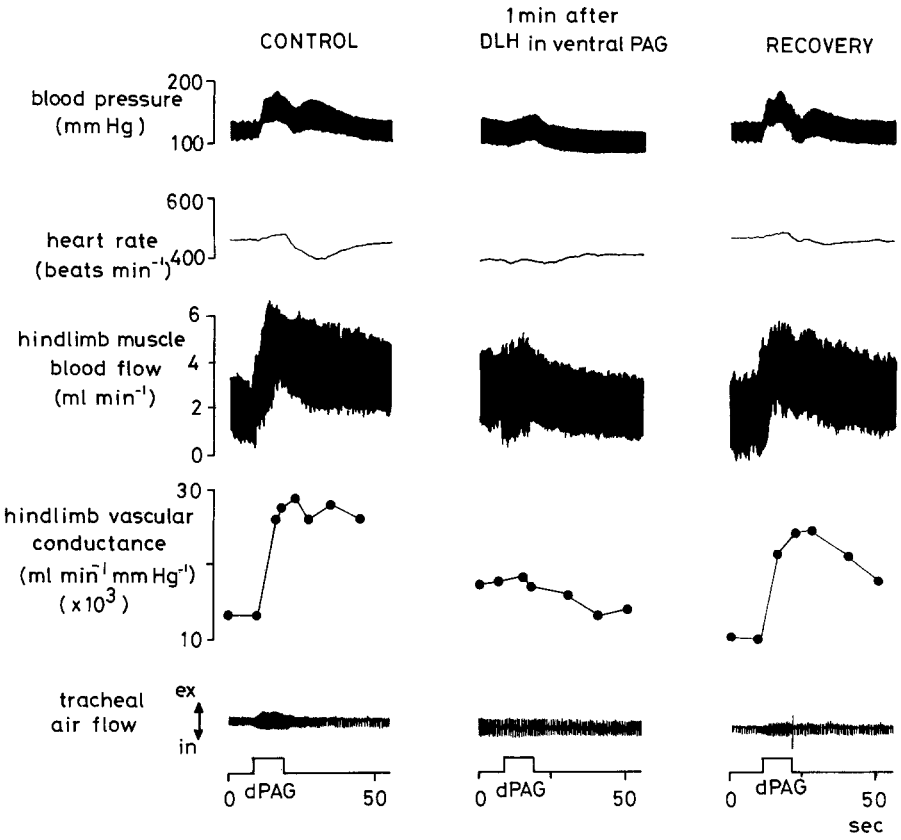

Fig. 4. Effect of injection of DLH into the ventrolateral PAG on the cardiovascular defence response evoked by stimulation in the dorsal PAG. Left panel shows typical "defense" pattern of cardiovascular response evoked by stimulation in the dorsal PAG during the control period (60 μA, 0.5 ms pulses at 80 Hz). Middle panel: all the components of the response were depressed 1 min after injection of DLH into the ventrolateral PAG. Right hand panel: recovery of the response 20 min later

level of the decussation of the superior cerebellar peduncle, approximately 7.5–8.0 mm caudal to Bregma (Fig. 6). Injections made rostral or caudal to this level or into the PAG on a level with or dorsal to the aqueduct (Fig. 6) failed to produce any consistent change in the cardiovascular response to stimulation in the dorsal PAG. Similarly, injections made into the dorsal raphe nucleus, which bounds the caudal part of the PAG on its medial side, also failed to attenuate the response to stimulation in the midbrain defense area.

Effect of injection of DLH into the ventrolateral PAG on the cardiovascular response to stimulation in the RVLM

Since injection of DLH into the ventral PAG produced changes in resting cardiovascular variables (see above) it was possible that the reduction in the defense response might have been due to summation of the excitatory (pressor) and inhibitory (depressor) effects produced simultaneously by stimulation in the dorsolateral and ventrolateral parts of the PAG. To control for this, the effect of microinjection of DLH into the ventrolateral PAG was tested on the pressor response evoked by stimulation in the rostral ventrolateral medulla (RVLM). Injections were made into the ventrolateral PAG at 6 sites where DLH would have been expected to attenuate the response evoked from the dorsal PAG (Fig. 7C). However, despite the fact that stimulation at these sites produced a fall in resting blood pressure, the pressor response to stimulation in the RVLM remained unchanged (Fig. 7C).

Injection of saline into the ventrolateral PAG

To control for non-specific changes induced by the injection of DLH 0.3 μl saline was injected at 5 sites in the ventral half of the caudal PAG (Fig. 7B). These injections did not produce any significant change in the cardiovascular defence response to stimulation in the dorsal PAG, or on resting cardiovascular variables.

Discussion

In the present study microinjection of DLH into a restricted part of the ventrolateral PAG significantly attenuated the cardiovascular components of the defense response evoked by stimulation in the dorsal PAG. Before the significance of this finding can be assessed it is important to eliminate a number of potential sources of error which are inherent in the methodology. The volume of fluid injected into the ventral PAG in these experiments was relatively large (300–500 nl). In addition, the sites of electrical stimulation in the dorsal PAG were only 1–3 mm away from the centre of the microinjections in the ventrolateral PAG. Thus displacement of tissue by the volume of the injection, or a change in composition of the

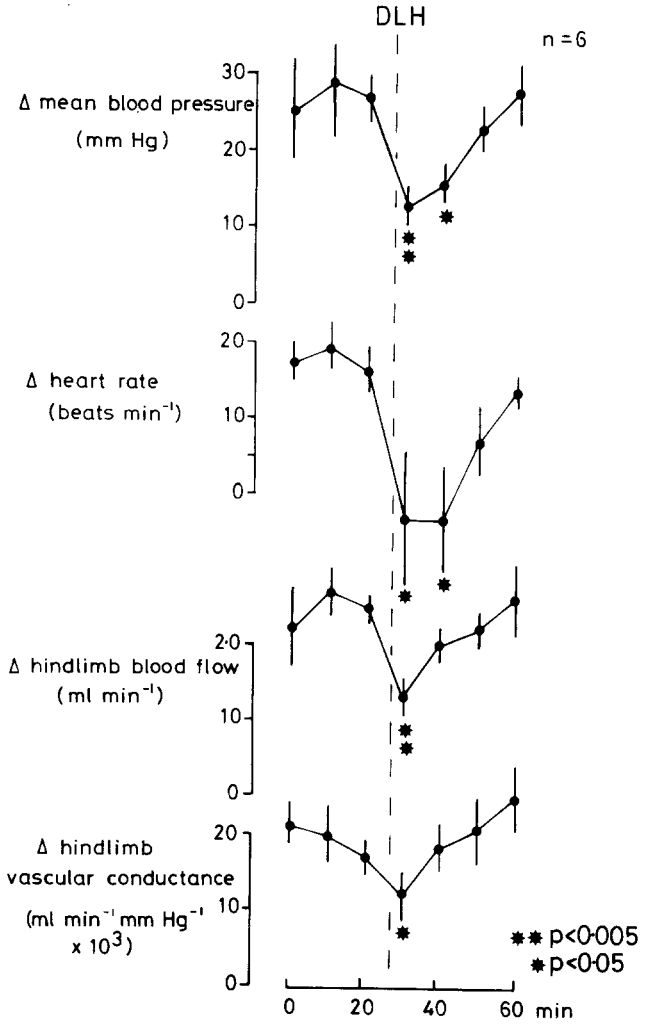

Fig. 5. Effect of microinjection of DLH into ventrolateral PAG (at time indicated by broken line) on the magnitude of the pressor response, tachycardia, increase in muscle blood flow and conductance evoked by electrical stimulation in the dorsal PAG. Data (means ± SE) taken from the 6 effective injections shown as filled circles in Fig. 6

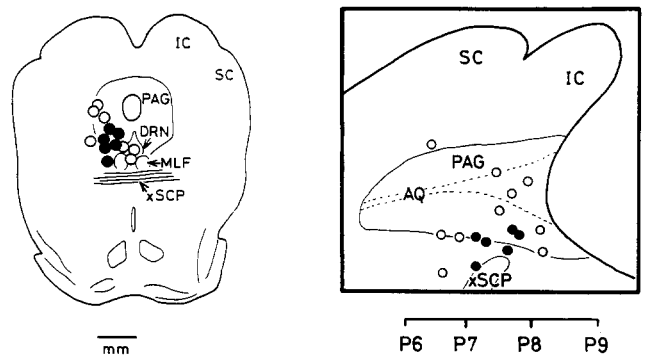

Fig. 6. Distribution of DLH injection sites within the PAG. Right hand panel shows parasaggittal section through the midbrain approximately 900 μm lateral to the midline. Broken line shows level of cerebral aqueduct. Only injection sites located within 500–1250 μm lateral to the midline have been plotted. Filled circles: sites where injection of DLH attenuated the defence response evoked by stimulation in the dorsal PAG. Open circles: sites of injections which did not affect the defence response. Coronal section on the left at approximately P7.8 shows distribution in the mediolateral plane, of all injections of DLH made between 7.5 and 8.5 mm caudal to bregma. Abbreviations as in Figs. 1 and 3

extracellular fluid around the stimulating electrode produced by fluid diffusing away from the injection site, might have temporarily reduced the effectiveness of the electrical stimulus in the dorsal PAG. This explanation seems unlikely however, since many injections of DLH made close to the electrical stimulation sites failed to attenuate the defence response. Furthermore, injections of similar volumes of saline into the "effective" region in the ventrolateral PAG also failed to alter the defence response.

Another potential source of artifact arises from the fact that injection of DLH at effective sites in the ventrolateral PAG always produced a decrease in resting blood pressure and heart rate and vasodilatation in the hindlimb. Thus it is possible that during the period of sympathoinhibition, the cardiovascular system could have been less responsive to stimulation in the dorsal PAG. Alternatively, summation of sympathoexcitatory and sympathoinhibitory influences arriving simultaneously at the spinal sympathetic outflow could have resulted in a reduction in the size of the defence response. However, neither of these explanations seems likely since many of the microinjections of DLH which failed to attenuate the defence response produced changes in resting cardiovascular variables which were similar to those seen at effective sites. Furthermore, injections of DLH into the "effective" area in the ventrolateral PAG had no effect on the pressor response evoked by electrical stimulation in the RVLM, despite the fact that resting blood pressure fell. It is unlikely therefore, that the inhibitory effects produced by injection of DLH at effective sites within the ventrolateral PAG were due to summation of sympathoinhibitory and sympathoexcitatory effects at the level of sympathetic preganglionic neurones.

The efferent pathway for the cardiovascular components of the defence response is known to relay on spinally projecting neurones in the RVLM which in turn terminate on sympathetic preganglionic neurones in the intermediolateral cell column (Lovick et al. 1984; Carrive et al. 1988). Modulation of activity in the defence pathway by the ventrolateral PAG could therefore occur at the level of the synaptic relay in the RVLM. Recent electrophysiological studies have shown that activation of neurones in the ventrolateral PAG can inhibit the activity of spinally-projecting neurones in the RVLM (Lovick 1991b). On the basis of this finding it might be expected that electrical stimulation of neurones in the RVLM would be less effective after microinjection of DLH into the ventrolateral PAG. However, electrical stimulation in the RVLM, especially at the suprathreshold intensities necessary to evoke a consistent pressor response of around 30 mm Hg (see Fig. 7C) would activate passing axons as well as perikarya of bulbospinal neurones. Thus the effectiveness of electrical stimulation in the RVLM may not have been substantially altered by synaptically-mediated changes in the excitability of nerve cell bodies in the RVLM.

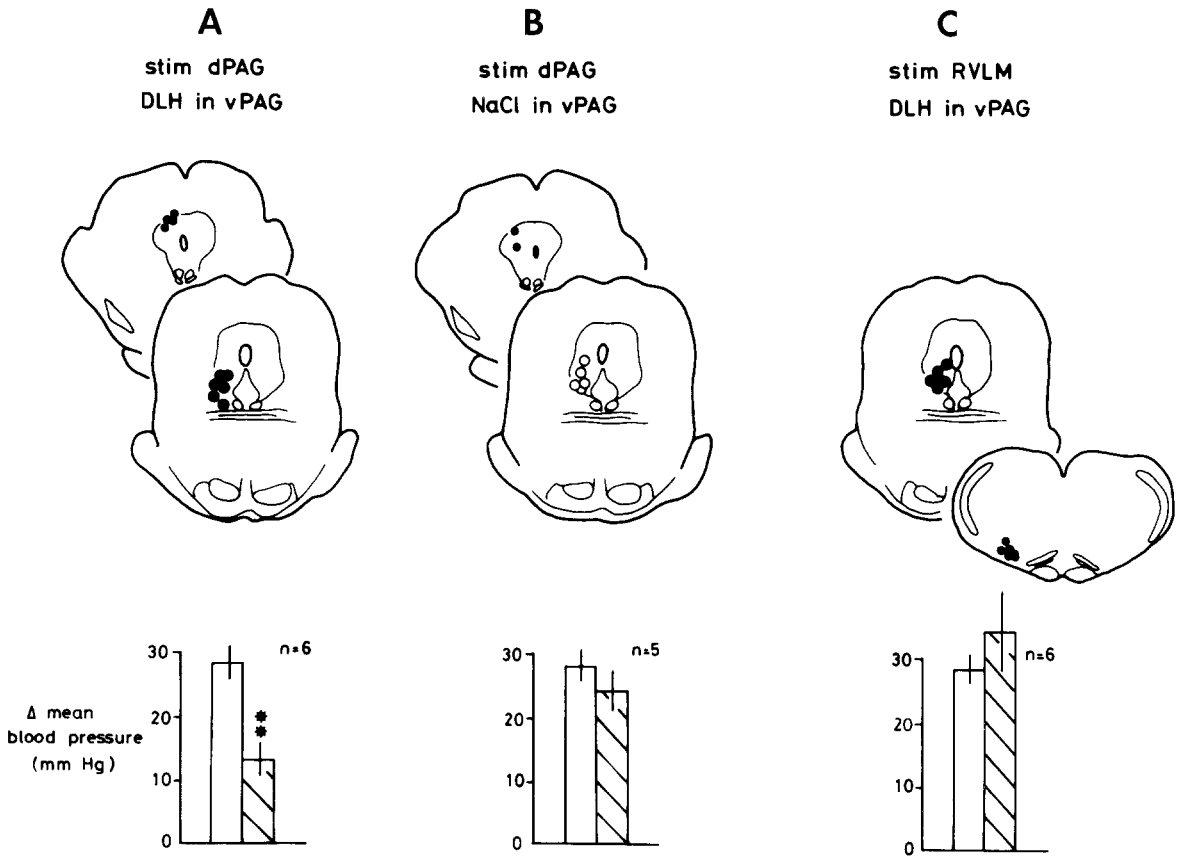

Fig. 7. **A** Histogram to show inhibition of the pressor component of the defence response evoked by stimulation in the dorsal PAG produced by injection of DLH into the 6 effective sites in the ventrolateral PAG. Open bar: control pressor response, hatched bar 1.5 min after injection of DLH. Means ± SE, ** $p < 0.005$. Outline drawings show stimulation sites (upper section) and microinjection sites (lower sections) in the PAG. **B** Injection of saline into the ventrolateral PAG (5 sites, open circles) had no effect on the pressor response evoked from the dorsal PAG. **C** Injection of DLH into the ventrolateral PAG (6 sites) had no effect on the pressor response evoked by electrical stimulation in the RVLM

The pathway by which the ventrolateral PAG produces its inhibitory effects in the RVLM is not clear. Most studies of afferent input to the RVLM from the PAG have reported that it arises from neurones situated on a level with and dorsal to the aqueduct (Andrezik et al. 1981; Lovick 1986; Li and Lovick 1985). However, in a more recent retrograde tracing study in the cat (Carrive and Bandler 1990), labelled cells were also found in a region of the PAG which overlaps part of the effective modulatory region in the ventrolateral PAG described in the present experiments in the rat. Thus there could be a direct effect of ventrolateral PAG neurones on rostral ventrolateral medullary cells. A second possibility is that activity in the RVLM is modulated by an indirect pathway from the ventrolateral PAG via the medullary raphe nuclei. The ventrolateral PAG sends direct excitatory projections to the medullary raphe nuclei (e.g. Lovick et al. 1978). In turn, nucleus raphe magnus and raphe pallidus project to the RVLM (Andrezik et al. 1981; Lovick 1986; Nicholas and Hancock 1990) and electrophysiological experiments have indicated that the projection from nucleus raphe magnus at least, is largely inhibitory (Lovick 1988). Thus both direct and indirect pathways from the ventrolateral PAG to the RVLM could contribute to the inhibitory modulation of activity in the descending efferent pathway from the defence area in the dorsal PAG.

The results of the present study provide direct evidence which supports the hypothesis advanced by Huangfu and Li (1987) that neurones in the ventral PAG exert an inhibitory influence on the cardiovascular defence response. In the rat, the effective cells appear to be localised in the ventrolateral portion of the PAG at the level of the decussation of the superior cerebellar peduncle. The functional role of the ventrolateral PAG in cardiovascular regulation is intriguing. There are several indications that the dorsal and ventrolateral parts of the PAG produce opposing effects, not only in terms of cardiovascular regulation but also with regard to somatomotor and behavioural activity. Neurones in the dorsal half of the PAG are known to integrate the complex pattern of behavioural and cardiovascular changes which are characteristic of an animals response to danger (Bandler et al. 1991). On the other hand, activation of neurones in the ventrolateral PAG can be positively reinforcing and produce immobility and sympathoinhibition (Liebman et al. 1973; Dennis et al. 1980; Carrive and Bandler 1990; Zhang

et al. 1990). Stressful or fear-inducing encounters which lead to active defensive behaviour are often followed by a period of sympathoinhibition and inactivity, during which the animal undergoes a period of rest and recuperation (Bolles and Fanselow 1980). It has recently been suggested that the ventrolateral PAG may be involved in mediating this type of recuperative behaviour (Lovick 1991a). The inhibitory modulation by the ventrolateral PAG of activity in the efferent pathway for the cardiovascular components of the defence response could therefore be a strategy which acts to limit active defense responses and allows the cardiovascular components of recuperative behaviour to predominate.

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