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THE PONTO-MEDULLARY AREA INTEGRATING THE DEFENCE REACTION IN THE CAT AND ITS INFLUENCE ON MUSCLE BLOOD FLOW

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SUMMARY

1. In anaesthetized cats the effects were investigated of electrical stimulation of regions in the caudal mesencephalon, pons and medulla on muscle blood flow, skin blood flow and arterial blood pressure.

2. It was found that within the dorsal part of the well known pressor area there is a narrow strip, 2·5 mm lateral from the mid line, starting ventral to the inferior colliculus and ending in the medulla close to the floor of the IV ventricle, from which vasodilatation in skeletal muscles is selectively obtained. This strip is quite separate from the more ventral, efferent pathway for *active* vasodilatation running from the hypothalamic and rostral mesencephalic 'defence centre'.

3. As in the case of the hypothalamic and rostral mesencephalic 'defence centre', the muscle vasodilatation obtained from the caudal strip is accompanied not only by a rise of arterial blood pressure, but also by tachycardia, vasoconstriction in the skin, pupillary dilatation and piloerection.

4. Stimulation, restricted to the caudal strip, via implanted electrodes in unanaesthetized animals, produced a behavioural response resembling the defence reaction. The strip, therefore, is probably a caudal extension of the 'defence centre'.

5. Unlike the vasodilatation elicited from the more rostral part of the 'defence centre' in the hypothalamus and mesencephalon, the muscle vasodilatation obtained on stimulation of the caudal strip was resistant to atropine, but was blocked by guanethidine.

6. It is suggested that during naturally occurring defence reactions in the normal animal the ponto-medullary area is activated together with the hypothalamo-mesencephalic area, inhibition of vasoconstrictor tone then accompanying activation of the vasodilator nerve fibres in skeletal muscle.

INTRODUCTION

Some years ago it was shown that the regions in the diencephalon and mesencephalon which integrate the somatic movements characteristic of the defence reaction play a similar part with regard to the cardiovascular and other visceral components of the response, and the conclusion was drawn that these regions of the brain stem could be regarded together as the reflex centre for the reaction (Abrahams, Hilton & Zbrożyna, 1960). Nevertheless, as was indicated at the time, there is evidence that the integrative region extends further caudally, for Keller (1932) had obtained what he regarded as typical rage reactions in response to a mild stimulus in cats chronically decerebrated just rostral to the beginning of the pons, and Bard & Macht (1958) had reported many features of the defence reaction in response to strong noxious stimulation in preparations in which the decerebration had been carried out so far caudally as to remove even the rostral part of the pons.

In spite of information of this kind, the prevalent view of the role of the lower brain stem has been that it controls isolated autonomic functions and that it has little or no capability of organizing these into patterns of response. However, as the present investigation has shown, electrical stimulation within a small and sharply localized strip, running on either side of the mid line, well into the medulla and almost reaching the floor of the IV ventricle, can elicit a pattern of behavioural and visceral response which is characteristic of the defence reaction. From these results, which were reported briefly by Coote, Hilton & Zbrożyna (1967), and are here given in full, it may be concluded that the integrative region for the defence reaction runs the whole length of the brain stem, from the hypothalamus rostrally to the medulla caudally, though the precise part played by each may differ slightly according to its location.

METHODS

The experiments were performed on fifty-eight cats. The acute experiments were carried out under chloralose anaesthesia (60–80 mg/kg given I.V.) after induction with ethyl chloride and ether. The preparations for recording skin and hind limb muscle blood flow were as previously described (Abrahams *et al.* 1960). In a few experiments, instead of skin blood flow, paw volume was registered using the technique of plethysmography described by Prout, Coote & Downman (1964). Arterial blood pressure was recorded via a polyethylene cannula inserted into a carotid artery and connected to a pressure transducer (Bell & Howell). Respiration was recorded using a mercury-in-rubber strain gauge strapped around the chest. All the strain gauge recording instruments were connected to a bridge amplifier and displayed each on one channel of a pen-recorder (Offner or Devices). Heart-rate was recorded by feeding the electronic analogue of the arterial pressure pulse into a rate-meter,

the output of which was displayed on one channel of the pen recorder. Respiratory movements were prevented in some animals by intravenous injection of gallamine triethiodide (Flaxedil, 10 mg/kg) after which the animal was maintained on positive pressure, artificial respiration.

Deep structures of the brain stem were stimulated by the use of stereotactically placed monopolar electrodes prepared from stainless-steel sewing needles varnished except for 20–50 μm at the tip with four coats of Araldite 985E. For insertion behind the tentorium into the caudal brain stem the electrode was held in a manipulator tilted at 45° to the vertical axis. The indifferent electrode was a steel clip attached to the reflected temporal muscle. Square-wave stimuli of 2 msec duration, 70 Hz and 50–200 μA were delivered via isolation units from a Grass S8 multifunction stimulator. Current was monitored throughout the stimulation period by measuring the voltage drop across a 1 kΩ resistor placed in series with the stimulator output.

In seven cats electrodes were implanted into the brain stem in sterile operations under pentobarbitone anaesthesia, as described previously (Abrahams *et al.* 1960). At the end of each experiment the exact location of the electrodes was determined histologically. The brain was fixed by perfusion with alcoholic formol saline. Sections 25 μm thick were cut on a freezing microtome, and stained with luxol fast blue and cresyl violet (Klüver & Barrera, 1953).

RESULTS

In anaesthetized cats regions in the caudal mesencephalon, pons and medulla were stimulated electrically, and muscle and skin blood flow, arterial blood pressure, heart rate and respiration were recorded. The pattern of response varied, depending on the area stimulated. Within the well known pressor area of the caudal brain stem, stimulation usually elicited increased resistance to flow in the vascular bed of skeletal muscle (i.e. vasoconstriction), together with a similar change in the skin. Such a vasoconstrictor response in skeletal muscle is illustrated in Fig. 1. Occasionally, dilatation of resistance vessels in the skin was elicited, sometimes accompanied by vasoconstriction and sometimes with no change in the vascular bed of skeletal muscle. But the points which were sought after and plotted in this investigation were those from which dilatation of resistance vessels in skeletal muscle was obtained. These points also were all in the pressor area, and a record of a typical response is shown in Fig. 2.

As in the earlier study of the vasodilator responses to electrical stimulation in the hypothalamus and mid-brain (Abrahams *et al.* 1960) it was clear that the blood pressure rises made little contribution to the increase in muscle blood flow; for the rise of blood pressure had largely subsided before the increase in flow, and it had returned to normal before the hyperaemia reached its peak. The increase in muscle blood flow had a variable latency to onset; it sometimes started during the 15 sec period of brain stem stimulation, though often after it was terminated. The peak of the vasodilatation was reached 20–40 sec after stimulation had been commenced. The calculated decrease in resistance in the muscle vascular

bed was 20–70 % in different tests in different experiments. Stimulation at points from which this muscle vasodilatation was obtained always elicited vasoconstriction in the skin, recorded as a decrease in either blood flow or paw-volume (Fig. 3). These were accompanied by an increase in pulse pressure as well as mean arterial pressure, usually with a tachycardia.

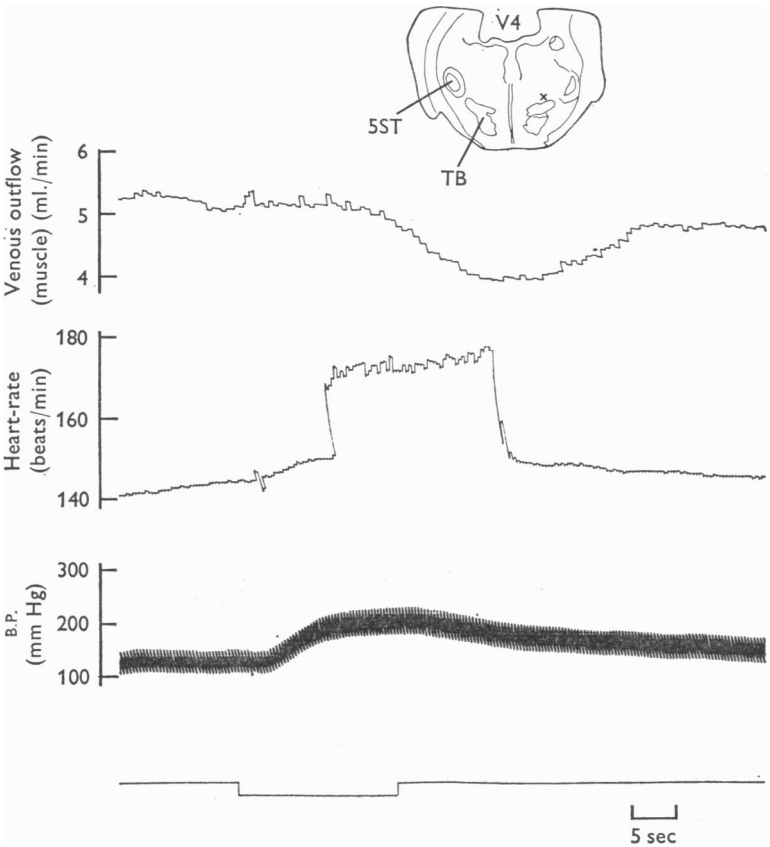

Fig. 1. Cat, chloralose. Records of venous outflow from skinned lower leg (top), heart-rate (middle) and arterial blood pressure (bottom). Cross on coronal section of brain stem shows location of electrode tip; period of stimulation shown by deflexion on signal line. Symbols on coronal section are as for Fig. 4.

This pattern of cardiovascular response was accompanied by hyperpnoea, dilatation of the pupils and piloerection. Indeed, the whole response resembled that characteristic of the defence reaction, as previously obtained on electrical stimulation of the appropriate regions of the hypothalamus and mid-brain (Abrahams *et al.* 1960).

Location of the caudal brain stem area

The caudal brain stem area from which muscle vasodilatation was obtained was about 0·5 mm across and lay 2·5 mm lateral to the mid line, on both sides, extending through the caudal mesencephalon and pons, to the medulla. This is shown on the schematic dorsal view of the caudal

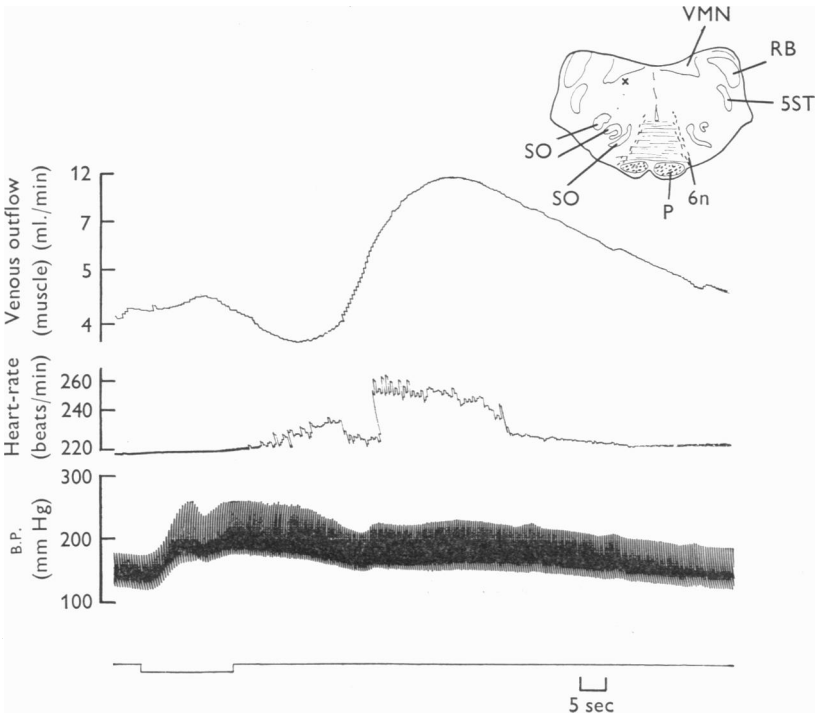

Fig. 2. Cat, chloralose. Records of venous outflow from skinned hind limb (top), heart rate (middle) and arterial blood pressure (bottom). Cross on coronal section of the brain stem shows location of electrode tip; period of stimulation indicated by deflexion on signal line. Symbols on coronal sections of the brain stem as on Fig. 4.

brain stem of Fig. 5. Further detail is given in the sagittal and coronal sections of Fig. 4, from which it is seen that the area occupies a relatively dorsal position. At the level of the caudal mesencephalon, it lies where the cuneiform nucleus borders on the central grey matter (level *A*), almost as a caudal extension of the region in the lateral tegmentum demarcated in the earlier investigation of Abrahams *et al.* (1960), which seemingly ends abruptly as the dorsal part of the central grey matter tails off. From here it extends into the most dorsal part of the reticular formation medial

to the brachium conjunctivum, just lateral to the nucleus coeruleus (levels *B*, *C* and *D*). In the pons the area becomes more extensive dorso-ventrally, occupying the most dorsal part of the reticular formation (levels *E* and *F*). More caudally still it lies even more ventrally, in the lateral part of the reticular formation. In the medulla it lies on the level of

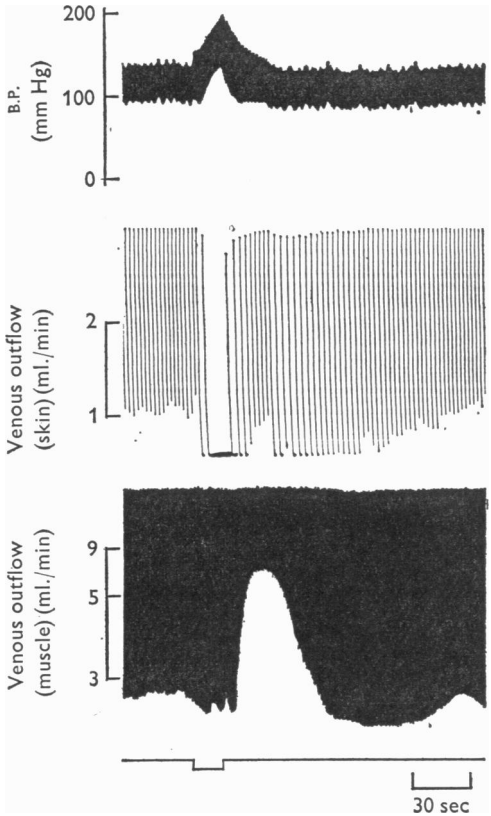

Fig. 3. Cat, chloralose. Records of arterial blood pressure (top), venous outflow from right cephalic vein (middle) and venous outflow from skinned hind limb (bottom). Signal marker indicates period of stimulation in the caudal vasodilator area.

the genu of the facial nerve (level *G*) from which it extends ventrally as a narrow strip into the reticular formation. From here the area occupies the dorsal part of the nucleus reticularis parvocellularis lying ventral to the medial vestibular nucleus (levels *H* and *I*). In its most caudal part it appears to encroach on the medial vestibular nucleus before finally tailing off in the dorsal medullary reticular formation close to the floor of the IV ventricle (level *J*).

Stimulation outside this strip occasionally produced muscle blood flow increases which followed a large increase in resistance and were small. Large vasodilator responses were obtained on stimulation of the ventral vasodilator pathway from the hypothalamic and mid-brain centres for the defence reaction, previously described by Lindgren & Uvnäs (1953) and Abrahams *et al.* (1960). These are the most ventral points, lateral to the trapezoid body, mapped at levels *F*, *G* and *H* and also seen at levels *D* and *I*.

The peripheral nervous mechanism of the muscle vasodilatation

In the cat, the muscle vasodilatation elicited by electrical stimulation of the hypothalamic and mid-brain regions integrating the defence reaction is brought about mainly by cholinergic vasodilator nerve fibres, since it is greatly reduced, or abolished, by atropine. It was therefore important to establish whether the vasodilatation elicited from the more caudal brain stem is mediated in the same way. It was found that atropine, even in the large doses (1 mg/kg) which abolish the muscle vasodilatation elicited by hypothalamic stimulation, had no effect on the muscle vasodilatation produced by stimulation in the area located in the caudal brain stem (Fig. 6*B*). By contrast with the lack of effect on the muscle vasodilatation elicited from the caudal strip, that elicited by stimulation of the ventral pathway was always blocked by atropine. However, guanethidine (3 mg/kg) given I.V. abolished the vasodilatation produced by stimulation in the caudal strip (Fig. 6*C*, *D*). Abolition of the vasodilatation by guanethidine also excluded muscular contraction as a cause for the increased flow; this was confirmed by the occurrence of a normal vasodilatation in animals which had been paralysed with Flaxedil. In further experiments the possibility was tested that a significant contribution to the muscle vasodilatation was made by secretion of adrenaline from the adrenal medulla. The splanchnic nerves were sectioned on both sides, after which the muscle vasodilatation was little changed.

It was thus clear that the muscle vasodilatation resulted from inhibition of vasoconstrictor tone. The question remaining was whether this was a direct effect of electrical stimulation within the caudal strip, or whether it arose indirectly as part of a baroreceptor reflex following the increase in arterial blood pressure. The latter possibility was tested by stimulating within the caudal strip in a preparation with both vagi sectioned, before and after occluding the carotid arteries. As shown in Fig. 7, the muscle vasodilatation was hardly affected by elimination of the baroreceptor input: relative to the base-line level of vasoconstrictor tone before brain stem stimulation, the inhibition of vasoconstriction seemed as great without as with functioning baroreceptor areas.

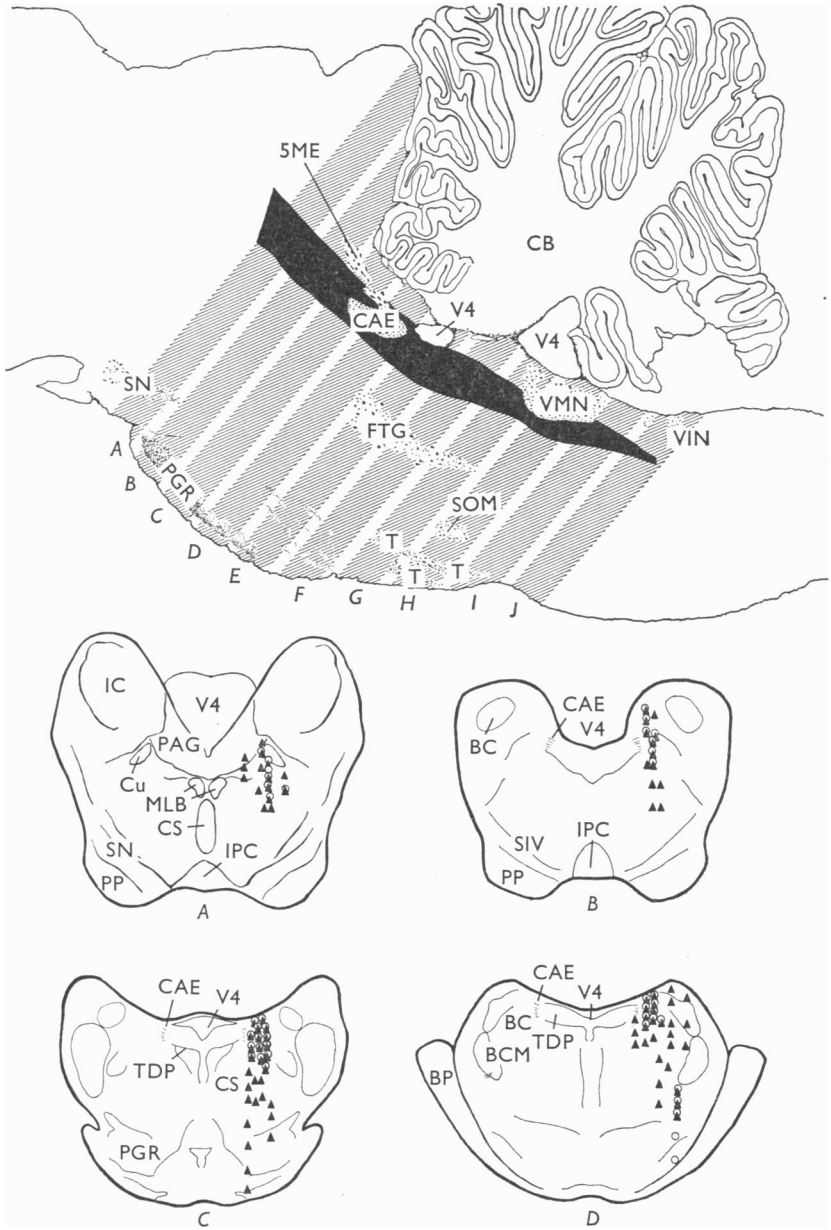

Fig. 4. For legend see facing page.

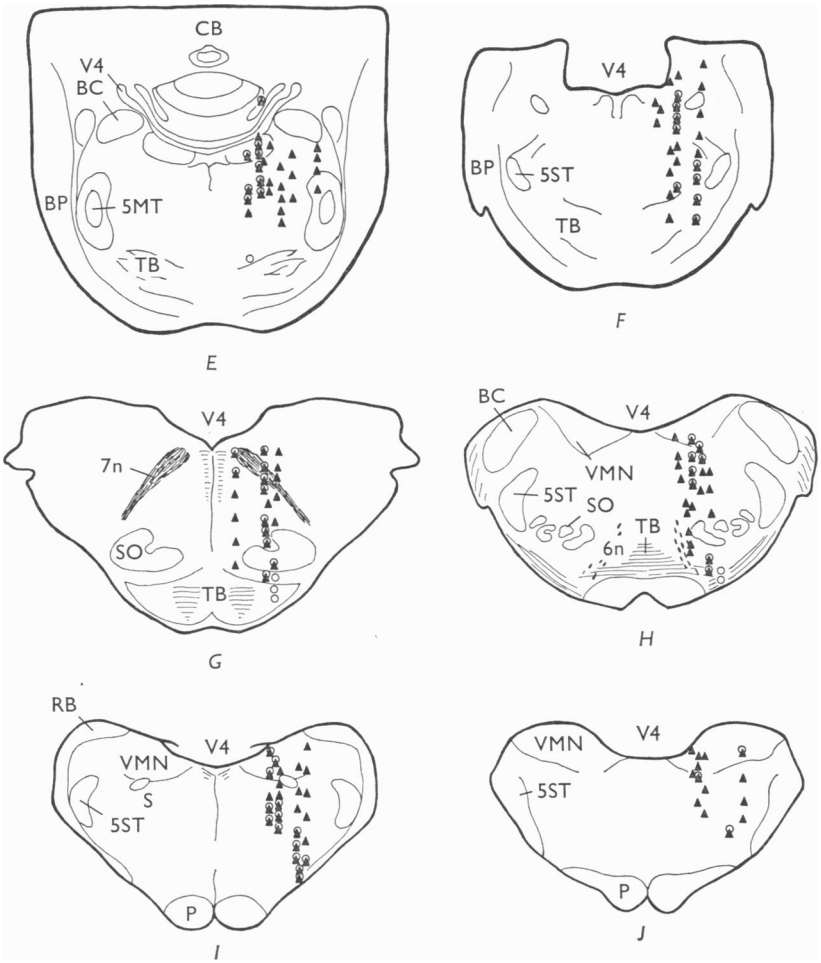

Fig. 4. Above, parasagittal section of caudal brain stem 2·5 mm lateral to mid line. Black area indicates location of area from which muscle vasodilatation is obtained. Hatched strips show levels of sections *A*–*J*.

Triangles indicate points from which increases in arterial blood pressure were obtained without muscle vasodilatation; open circles show points from which muscle vasodilatation was obtained in addition. 3N, oculomotor nerve; 4N, nucleus of the trochlear nerve; 5ME, mesencephalic trigeminal nucleus; 5MET, mesencephalic trigeminal tract; 5MT, motor trigeminal tract; 5ST, spinal trigeminal tract; 6N, nucleus of the abducens; 6n, abducens nerve; 7N, nucleus of the facial nerve; 7n, facial nerve; BC, brachium conjunctive; BCM, marginal nucleus of the brachium conjunctive; BP, brachium pontis; CAE, nucleus caeruleus; CB, cerebellum; CS, superior central nucleus; Cu, cuneiform nucleus; FTG, gigantocellular tegmental field; IC, inferior colliculus; IPC, central interpeduncular nucleus; MLB, medial longitudinal bundle; P, pyramidal tract; PAG, periaqueductal grey; PGR, pontine grey; PP, pes pedunculi; RB, restiform body; S, solitary tract; SN, substantia nigra; SO nucleus of the superior olive; SOM, medial nucleus of the superior olive; T, nucleus of the trapezoid body; TB, trapezoid body; TDP, dorsal tegmental nucleus; V4, fourth ventricle; VIN, inferior vestibular nucleus; VMN, medial vestibular nucleus.

Stimulation in the pons and medulla of unanaesthetized cats

In eight cats, sets of two to five electrodes were implanted with their tips in the pons and medulla. The effect on their behaviour of stimulation via these electrodes was tested 2–3 days after implantation.

Stimulation through electrodes which had been implanted within the caudal strip produced in the conscious animals a response in many ways resembling the defence reaction: there was a flattening of the ears, pupillary dilatation, and piloerection along the tail, sometimes with growling or

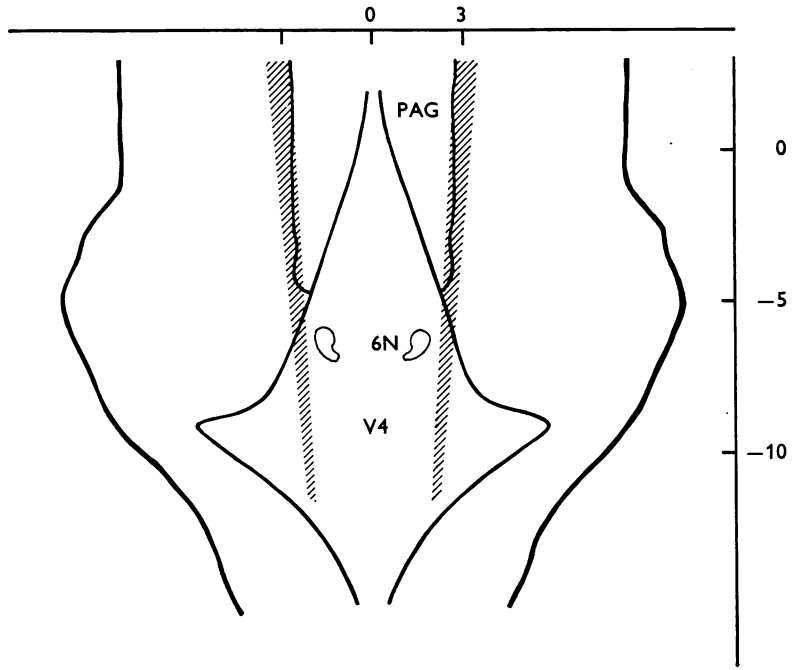

Fig. 5. Diagrammatic dorsal view of floor of fourth ventricle showing area (shaded) in the lower brain stem from which muscle vasodilatation is obtained. Symbols as in Fig. 4.

hissing, running or crouching movements and extension of the claws. The whole response did not appear to be as fully or as vigorously expressed as the defence reaction obtained from the appropriate regions in the hypothalamus or mid-brain, and was usually accompanied by turning towards the stimulated side. In these animals subsequent investigation under chloralose anaesthesia of the cardiovascular changes on electrical stimulation via the same electrodes showed a similar pattern of response to that obtained in the earlier acute experiments on stimulation within the caudal strip. The reduction in vascular resistance in the hind limb was

usually more than 50 % and was not affected by I.V. injection of large doses of atropine, up to 1·0 mg/kg.

When the electrode tips were implanted outside the caudal strip a less complete defence reaction, or only isolated components, were elicited, and in these experiments muscle vasodilatation was not elicited subsequently by stimulation via the same electrodes under anaesthesia.

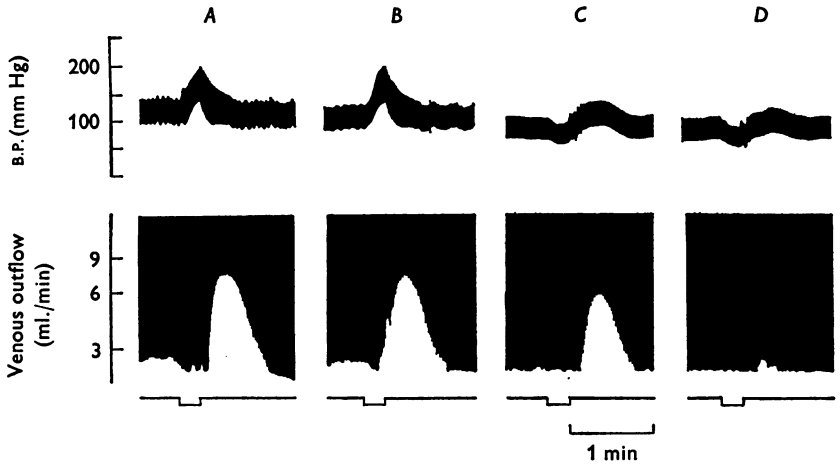

Fig. 6. Cat, chloralose. Records of arterial blood pressure (top), venous outflow from skinned lower leg (bottom). At signals, stimulation in caudal vasodilator area; *A*, before injection of atropine; *B*, 14 min after I.V. injection of atropine 1 mg/kg; *C*, 30 min after I.V. injection of guanethidine 3 mg/kg; *D*, 45 min after I.V. injection of guanethidine 3 mg/kg.

DISCUSSION

It was originally demonstrated by Eliasson, Folkow, Lindgren & Uvnäs (1951) that the sympathetic vasodilator nerve fibres supplying the resistance vessels of skeletal muscle in the cat are activated by electrical stimulation in the hypothalamus and mid-brain. Abrahams *et al.* (1960) concluded that the resulting vasodilatation is the most characteristic component of the defence reaction; for, in acute experiments in which localized electrical stimulation of the brain stem was being used, this vasodilatation provided the best index of those areas likely to be involved in the integration of the whole pattern of response. In the investigation of Abrahams *et al.* (1960) the mapping of the integrative centre for the defence reaction was not taken further caudally than the caudal extremity of the superior colliculus, though it was recognized that it might extend further, at least into the pons, in view of the responses which had been obtained

by Keller (1932) and Bard & Macht (1958) with chronic decerebrate preparations. Accordingly, the mapping has been extended in the present investigation into the pons and medulla, and results obtained which indicate that the region continues through the length of the caudal brain stem as a narrow strip within the dorsal tegmentum about 2·5 mm from the mid line. This conclusion is based on the findings, first, that electrical stimulation in this area in anaesthetized cats elicits a large dilatation of resistance vessels in skeletal muscle, together with an increase in arterial blood pressure and heart-rate, pupillary dilatation and piloerection; and secondly,

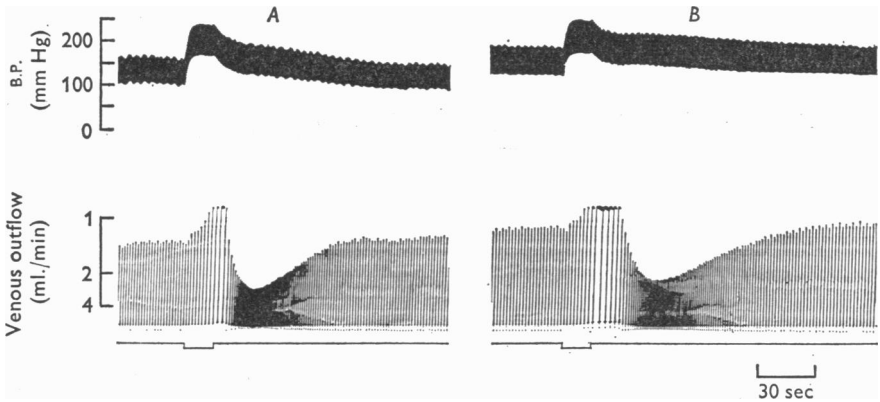

Fig. 7. Cat, chloralose, both vagi sectioned. Records of arterial blood pressure (top) and of venous outflow from skinned hind limb (bottom). At signals, stimulation in caudal vasodilator area before (*A*) and after (*B*) bilateral carotid occlusion.

that stimulation in the same area in conscious animals produces an appearance of agitation, with running or crawling, extended claws and sometimes growling, naturally also with pupillary dilatation and piloerection. This response resembles, in both its behavioural and autonomic aspects, the defence reaction evoked by hypothalamic or mesencephalic stimulation, or indeed by natural stimulation. The difference is that the hypothalamic or mesencephalic defence reaction is so very similar to the naturally occurring response, while medullary stimulation produces a response which is not so vigorous or so well integrated.

An important similarity in the experimental findings is that electrical stimulation has to be applied precisely in the localized region to produce the pattern of response. The findings indicate that this area is contiguous at its most rostral extent (ventral to the inferior colliculus) with the caudal part of the area previously defined (in the lateral tegmentum, ventral to the superior colliculus) and that it is a sharply localized strip which finally

tails off in the dorsal medulla close to the floor of the IV ventricle in the region commonly designated as the vasomotor centre.

A particular feature of the muscle vasodilatation elicited in the present experiments is that it is atropine-resistant and therefore does not depend to any significant extent on the activation of cholinergic vasodilator fibres. It occurs later than the active muscle vasodilatation seen in earlier experiments on hypothalamic stimulation (Abrahams *et al.* 1960), not always starting during the standard 15 sec period of electrical stimulation. This latency might be taken to indicate that a multineurone pathway is involved in this response. It would not then be surprising that the latency exhibited the marked variability seen, from one experiment to another, in view of the known differences in sensitivity of neurones of the reticular formation to the action of general anaesthetics.

The muscle vasodilatation itself is greatly reduced, or abolished, by guanethidine and thus results from inhibition of vasoconstrictor tone. This vasoconstrictor inhibition is almost certainly a direct effect of brain stem stimulation, for it is only obtained when the electrode tip is within the caudal strip. Stimulation outside it leads to the same increase in arterial blood pressure, but always with active vasoconstriction in skeletal muscle. Moreover, after bilateral vagal section and clipping both carotid arteries to eliminate the baroreceptor input, the muscle vasodilatation was still a prominent feature of the response to brain stem stimulation. It is significant that Bolme, Ngai & Rosell (1967) obtained a similar result in experiments on the dog. The gracilis muscle was perfused at constant flow and it was found that, under these conditions, stimulation in the 'defence area' of the hypothalamus elicited a biphasic vasodilatation, of which only the first phase seemed to be atropine-sensitive. The second, atropine-resistant phase which followed the period of stimulation was still obtained after bilateral vagotomy and carotid occlusion.

In the present experiments on the skinned hind limb of the cat, only the atropine-resistant vasodilatation is obtained when the caudal strip is stimulated. There is every reason to believe that the extra-lemniscal afferent pathway, which has been shown to connect with the hypothalamic and mid-brain areas integrating the defence reaction (Abrahams, Hilton & Malcolm, 1962) would be at least as effective in exciting the caudal strip, located in the present experiments. Thus, during a defence reaction elicited by a sufficiently intense noxious stimulus in the normal, non-anaesthetized animal the whole brain stem area from the hypothalamus rostrally to the medulla caudally would be activated together, so that, in skeletal muscle, inhibition of the on-going vasoconstrictor activity would accompany activation of the vasodilator nerve supply. It can be seen from the records in the experiments of Abrahams, Hilton & Zbrożyna (1964) that the

increase in muscle blood flow caused by hypothalamic stimulation in the conscious cat is reduced but not abolished by atropine. Under the special conditions of general anaesthesia, it would not be surprising that there should be some separation of these two effector mechanisms, with one much more readily activated by rostral brain stem stimulation and one by stimulation of the caudal extension; but even then the separation may not always be complete, as evidenced by the original findings of Eliasson *et al.* (1951) that atropine sometimes only blocked the muscle vasodilatation resulting from hypothalamic stimulation to the extent of some 70%.

It may therefore be concluded that the complete pattern of cardiovascular response evoked by noxious stimulation is organized in the defence area of the brain stem. Reflex inhibition of vasoconstrictor fibre activity in skeletal muscle produced by baroreceptor excitation plays no part in the inhibition of on-going sympathetic activity demonstrated in the present experiments and so it is unlikely to be important for the effectiveness of the cholinergic vasodilator supply, as was postulated by Folkow and his co-workers (Folkow, Oberg & Rubinstein, 1964; Djojosugito, Folkow, Kylstra, Lisander & Tuttle, 1970; Kylstra & Lisander, 1970; Lisander, 1970). Indeed, we have never found that bilateral carotid occlusion, which eliminates the effect of carotid sinus reflex afferents and increases vasoconstrictor tone in muscle, makes any marked difference in the active vasodilatation obtained on hypothalamic stimulation (J. H. Coote, S. M. Hilton & A. W. Zbrożyna, unpublished observations). This is in keeping with the findings of Hilton (1963, 1965) that the baroreceptor reflex as a whole is reset during the defence reaction.

The conclusion that inhibition of the normal vasoconstrictor tone in skeletal muscle is part of the pattern of cardiovascular response elicited from the brain stem areas integrating the defence reaction is relevant to the recent observations of Bolme, Novotny, Uvnäs & Wright (1970) that, while there are cholinergic vasodilator nerve fibres supplying the skeletal muscles of the sheep, goat and fox (in addition to the cat and dog), there are none to those of the rat, badger, polecat, hare or a variety of monkeys. Likewise, though there is no doubt that muscle vasodilatation is an important component of the defence reaction in man, it is not always possible to reduce the dilatation by administering atropine, in which case it seems due to circulating catecholamines (Barcroft, Brod, Hejl, Hirsjärvi & Kitchin, 1960). It is therefore important to have established that vasoconstrictor inhibition in skeletal muscle is a component of the whole pattern of cardiovascular response and that, even in the cat in which the muscles have an effective cholinergic vasodilator supply, this inhibition of vasoconstrictor tone can lead to a prominent increase in blood flow. There is no obvious reason why the skeletal muscles of the cat, dog, fox, sheep and goat should

have a cholinergic vasodilator nerve supply, but its sparsity or absence in other species does not necessarily imply any essential difference in their patterns of cardiovascular response during the defence reaction.

The 'defence area' in the caudal brain stem is anatomically distinct from the efferent pathway for active, cholinergic vasodilatation leading from the areas in the hypothalamus and mid-brain. This pathway is located ventrally, at the mesencephalic level between the substantia nigra and the cerebral peduncles (Abrahams *et al.* 1960) and more caudally as a narrow longitudinal band lying 3–5 mm lateral to the mid line and 1–2 mm above the ventral surface of the brain stem (Lindgren & Uvnäs, 1953). This has been confirmed recently by Schramm & Bignall (1971). The caudal defence strip is also well away from the medial region of the caudal medulla known as the 'depressor area' from which electrical stimulation elicits inhibition of vasoconstrictor tone (Alexander, 1946), accompanied by inhibition of the sympathetic vasoconstrictor activity in all other vascular beds, and by inhibition of other autonomic and somatic effectors (Lim, Wang & Yi, 1938; Bach, 1952). The caudal defence area itself is only about 0·5 mm across but it lies lateral to the mid line in the dorsal pontine and medullary reticular formation. It is, in fact, within the region usually designated as the excitatory or pressor region and which, in the medulla at least, is commonly called the vasomotor centre. It was shown by Abrahams *et al.* (1962) that chloralose, which was the anaesthetic used in the present investigation, blocks at synapses between the extra-lemniscal afferent pathway and neurones of the integrative defence centre in the hypothalamus and mid-brain. Since the pattern of autonomic response characteristic of the alerting stage of the defence reaction cannot be obtained as a reflex in chloralose-anaesthetized preparations, the responses obtained on electrical stimulation, in the acute experiments of the present series, show that the caudal strip must be either part of the integrative centre for the defence reaction, or an efferent pathway from a more rostrally located area from which the characteristic cardiovascular and behavioural response would be elicited. The latter possibility seems most unlikely, for such an area has not been described and there are no anatomically recognizable fibre tracts within the particular area of the reticular formation. Moreover, stimulation of a pathway is more likely to produce dissociated components of the complete pattern of response as was found in the case of the pathway for cholinergic vasodilatation from the hypothalamus and mid-brain which runs in the ventrolateral brain stem (Lindgren & Uvnäs 1953; Abrahams *et al.* 1960; Schramm & Bignall, 1971).

The inhibitory effect on the vasomotor output is selective, affecting the vasoconstrictor tone in the vascular bed of skeletal muscle alone; for it is accompanied by active vasoconstriction in the skin, increases in mean

arterial pressure and pulse pressure, tachycardia, piloerection and pupillary dilatation. Outside this caudal strip, as already emphasized, electrical stimulation elicits similar pressor responses, but the pattern of accompanying responses is no longer the same, in particular there is usually activation of the vasoconstrictor supply to skeletal muscle. This gives reason to believe that the medulla is as highly organized into regions integrating patterns of response as is the mid-brain or hypothalamus. Part of the original evidence for the concept of a medullary vasomotor centre was the discovery of Ranson & Billingsley (1916) of pressor and depressor points in the floor of the IV ventricle. But when Chen, Lim, Wang & Yi (1936, 1937) and Lim *et al.* (1938) repeated these experiments, they measured not only arterial blood pressure, but also heart-rate, the size of the pupil and spleen, the tone in the bladder, small intestine and colon, and the blood sugar. They also looked for signs of pilo-erection, sweat gland activation, and effects on the bronchioles. So universal were the changes observed that they felt Ranson & Billingsley's pressor area to be really a sympatho-excitor region and their depressor area a sympatho-inhibitory region. The present results, like those of Hilton & Spyer (1971) on the hypothalamic representation of the centre for the baroreceptor reflex response, reinforce these early doubts that any part of the medulla is functioning as a general 'vasomotor' centre. On the contrary, it seems that the medulla can initiate various patterns of autonomic and behavioural response, in some of which vasomotor components will form only a part.

Part of this work was carried out while S. M. Hilton & A. W. Zbrożyna were members of the Scientific Staff at the National Institute for Medical Research.

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