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CHANGES IN REGIONAL BLOOD FLOW AND CARDIODYNAMICS EVOKED BY ELECTRICAL STIMULATION OF THE FASTIGIAL NUCLEUS IN THE CAT AND THEIR SIMILARITY TO ORTHOSTATIC REFLEXES

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SUMMARY

1. Changes in regional blood flow and cardiodynamics were measured in anaesthetized paralysed cats during electrical stimulation of the rostral fastigial nucleus.

2. Fastigial stimulation results in a graded, highly reproducible and stereotyped cardiovascular response characterized by (*a*) increased systolic, diastolic and mean arterial pressures without changes in central venous or occluded vein pressure, (*b*) decreased blood flow and increased vascular resistance in the axillary, renal, femoral and mesenteric arteries, increased flow without any change in vascular resistance in the common carotid artery, and increase in total peripheral resistance, (*c*) a small increase in heart rate and myocardial contractile force, decrease in calculated stroke volume, and no change in the cardiac output.

3. Changes in regional arterial flow were abolished by transection of sympathetic nerves or blockade of α-adrenergic receptors by systemic administration of phentolamine.

4. Changes in heart rate and myocardial contractility were abolished by stellate ganglionectomy or blockade of β-adrenergic receptors by propranolol.

5. No changes in pupillary diameter or retraction of the nictitating membrane were seen during fastigial stimulation with stimuli producing substantial changes in blood pressure.

6. The fastigial pressor response represents a highly reproducible, stereotyped, graded, and differentiated pattern of activation of sympathetic preganglionic neurones.

7. The pattern of cardiovascular effects of fastigial stimulation simulates the compensatory (orthostatic) reflex response to maintenance of an upright posture.

8. Fastigial stimulation appears to excite the neural network subserving orthostatic reflexes.

INTRODUCTION

Electrical stimulation restricted to the rostral fastigial nucleus in the cat can produce a marked elevation in blood pressure and an increase in the heart rate (Miura & Reis, 1969, 1970, 1971; Achari & Downman, 1969, 1970; Lisander & Martner, 1971). This response has been termed the fastigial pressor response (Miura & Reis, 1970). The nature of the associated changes in cardiovascular dynamics during the fastigial pressor response has only partially been characterized. Achari & Downman (1970) observed that the fastigial pressor response was associated with an adrenergically mediated decrease in the volume of the hind limb, kidney and intestine as well as pupillary dilatation, retraction of the nictitating membrane and an electrodermal response. These findings suggested that stimulation of the fastigial nucleus results in diffuse and widespread activation of the sympathetic nervous system. More recently Lisander & Martner (1971), estimating blood flow by measurement of the venous effluent, found that the response was differentiated, resembling in part the response to carotid occlusion. They did not however measure the cardiac output. The functional importance of the fastigial pressor response remains obscure.

If the fastigial pressor response consists of widespread sympathetic activation it would be unlike any pattern of cardiovascular response occurring to natural stimuli. However, further detailed analysis of the cardiodynamic changes characterizing the fastigial pressor response might provide a clue to its biological significance. In the present study, we have therefore attempted to define in detail by the use of relatively direct methods, the changes in regional blood flows, resistances, and pressures and the cardiodynamic events including heart rate, myocardial contractility and cardiac output characterizing the fastigial pressor response. We have found that the fastigial pressor response consists of a differentiated pattern of sympathetically mediated cardiovascular activity and that this pattern simulates that of the orthostatic cardiovascular reflexes elicited by maintenance of an upright posture. A preliminary report of this study has been published already (Doba & Reis, 1972*a*).

METHODS

A. General methods

Forty-five adult mongrel cats were anaesthetized with 1% α-chloralose (50 mg/kg I.V.) after induction with ether anaesthesia. After insertion of cannulae in the femoral or brachial artery, femoral vein, and trachea, the animal was placed in a rotating

stereotaxic frame with the head flexed at 45 degrees. The rectal temperature was maintained at 37° C by a thermostatically regulated infrared lamp. Since the experiments usually lasted no more than 4–5 hr the initial dose of anaesthetic was considered sufficient to ensure surgical anaesthesia throughout the course of the experiment.

B. Measurement of cardiovascular activity

(i) *Systemic blood pressure* was recorded from a polyethylene catheter threaded up the femoral or brachial artery and positioned respectively in the abdominal aorta or the aortic arch and connected to Statham P23Db transducer. The heart rate was computed from the blood pressure pulse by a cardiotachometer (Beckman 9857) and end-tidal CO_2, sampled through a fine catheter placed in the tracheal cannula, was recorded by an infra-red gas analyser (Beckman LD-1). All cardiovascular activity was displayed on a polygraph (Beckman Dynograph Recorder, 504A).

(ii) *Regional blood flow* was recorded by a square-wave electromagnetic flow meter (Carolina Medical Electronics, types 322 and 332). Flow probes (Carolina Medical Electronics, EP403R, EP404R) were applied to (*a*) the femoral artery just below the inguinal ligament (White & Ross, 1966); (*b*) the axillary artery at its junction with the aortic arch approached through a supraclavicular incision; (*c*) the renal arteries, approached retroperitoneally as described by Hoffer (1965) with care taken to avoid interruption of the renal nerves; (*d*) the superior mesenteric artery, approached through a mid line laparotomy with careful separation of the surrounding sympathetic nerve net to assure minimal damage to the nerves (Ross, 1967); (*e*) the common carotid artery, approached through a mid line incision in the neck with isolation of the artery from the connective tissue of the carotid sheath (Abel, Pierce & Guntheroth, 1963); (*f*) the external carotid artery, exposed by splitting sterno-cleidomastoid and retracting the digastric muscle; and (*g*) the ascending aorta, approached through a thoracotomy in which the sternum was split transversely at the level of the third intercostal space, the rib widely retracted, the pericardium incised, and the root of the aorta delivered for placement of the probe (Kumazawa, Baccelli, Guazzi, Mancia & Zanchetti, 1969). No more than two probes were inserted in the animal at any one time. However, in any one experiment flow changes in numerous beds might be sampled. Renal blood flow was never measured after a laparotomy since the operation may produce reflex effects on renal flow (Hoffer, 1965).

After placement of the flow probe, the appropriate incision was closed. Particular care was given to assure mechanical stability of the arterial probe. The zero level of the flowmeter was established *in situ* before and just after an experimental series by occluding the artery distally. At the termination of an experiment, the probes were calibrated by passing whole blood from a reservoir at several constant flow rates through the isolated arterial segment to which the probe was attached (Kumazawa *et al.* 1969). In all animals a ligature was tightly tied around the ankle or forepaw to eliminate blood flow to the foot pad. This assured that the femoral or axillary arterial flow reflected blood flow to muscle (Feigl & Folkow, 1963) and not skin. In some animals the limbs were skinned to further exclude cutaneous blood flow. In all instances mean blood flow was recorded through an integration circuit built into the flowmeter and having a time constant of 0·5 sec.

The mean arterial pressure (P_m) was derived from the formula $(P_s + 2P_d)/3$, where P_s was systolic pressure and P_d was diastolic pressure. Regional vascular resistance (RVR) was conventionally obtained from the formula; $RVR = P_m/F_m$, where F_m was mean blood flow in a given vascular bed.

(iii) *Cardiac output* was estimated either from the blood flow in the ascending aorta (Kumazawa *et al.* 1969) or by a thermal dilution technique (Fegler, 1954;

Korner, 1965; Folkow, Lisander, Tuttle & Wang, 1968). In the latter method a small thermistor (Model 14012A, Hewlett-Packard) was threaded down the common carotid artery to lodge at the aortic arch just above the aortic valve. The thermistor probe served as one arm of a Wheatstone bridge circuit with the remainder of the bridge having variable voltage and calibration resistance and contained in a coupler (Hewlett-Packard 350-15) mounted in the polygraph. The thermister was a special glass-coated element with a resistance logarithmically inversely proportional to temperature changes. Nominal resistance of the probe at 40 °C was 1200 Ω ± 5%. The thermistor probe was pre-calibrated by the manufacturer to a corresponding absolute temperature for each ohm increment of thermistor resistance over a range of 1·000–2·999 kΩ (equivalent to a temperature range of 15–45° C) and matched to a corresponding balancing resistance. 0·9% saline (1 ml.) at room temperature (Evonuk, Imig, Greenfield & Eckstein, 1961) was injected as a bolus into the right atrium from a catheter threaded down the jugular vein and the thermal dilution curve recorded. In the cat there is a significant recirculation of thermal indicator as evidenced by a change in the slope of the down stroke of the curve. To eliminate recirculation from the calculation the down stroke of the curve was corrected by re-plotting the curve on semi-logarithmic paper and the area measure by a planimeter. Cardiac output was calculated according to the method described by Korner (1965).

Calculation of the cardiac output was made from the following formula:

$$C.O. = \frac{Q_i \times (T_b - T_i) \times K}{t \times T_a},$$

where $C.O.$ = cardiac output in ml./min; Q_i = quantity of injectate in ml.; T_b = temperature of blood in degrees C; T_i = temperature of injectate in degrees; T_a = average temperature change; t = time in sec; $(t \times T_a)$ = area under curve; K = a constant;

$$K = \frac{\text{specific gravity of injectate} \times \text{specific heat of injectate} \times 60 \text{ (sec)}}{\text{specific gravity of blood} \times \text{specific heat of blood}},$$

$$K = \frac{1{\cdot}005 \times 0{\cdot}997}{1{\cdot}054 \times 0{\cdot}88} \times 60 = 64{\cdot}82.$$

The values for specific gravity and specific heat were obtained from the Handbook of Biological Data (1952) and the formula of Korner (1965).

(iv) *Ventricular contractile force* was measured by a strain gauge arch (Cotten & Bay, 1956) (resistance 120 Ω) attached to the right ventricular wall by silk sutures. Details of the construction of this instrument have been reported elsewhere (Boniface, Brodie & Waldon, 1953). The distance between the two legs of the arch is variable and ranges between a minimum of 15 and maximum of 30 mm. To obtain the maximum measurable contraction the arm distance was set at approximately 150% of the initial length (Cotten & Bay, 1956). The strain gauge arch was calibrated in terms of the gram weight required to produce a given deflexion of the pen on the polygraph. The instrument was connected through a strain gauge coupler (Beckman 9803) to the polygraph.

(v) *Central venous pressure* was measured through a polyethylene catheter inserted into the right atrium through the jugular or femoral vein. To obtain the occluded vein pressure in the femoral vein a pressure cuff was applied to the upper part of the thigh and inflated to a level above systolic pressure, around 250 mm Hg (Browse, Lorenz & Shepherd, 1966). A polyethylene catheter was inserted into the

vein distal to the site of occlusion and connected via a Statham P23Db transducer to the polygraph.

(vi) *Other manipulations.* The vagus nerve was sectioned in the neck. Transection of the cardiac nerves distal to the stellate ganglion was performed through a thoracotomy as described above. The renal nerves were transected through a retroperitoneal approach and the femoral artery was denervated by section of both the sciatic and femoral nerves (White & Ross, 1966). Pupillary size and retraction of the nictitating membrane were estimated by visual observation and in some cases documented by photography.

C. Stimulation of the fastigial nucleus

The rostral and ventromedial quadrant of the fastigial nucleus, the site at which a fastigial pressor response is evoked (Miura & Reis, 1969), was stimulated electrically through a thin monopolar electrode consisting of a stainless-steel wire (diameter 0·006 in.) coated with teflon and bared at the tip for 0·3 mm and carried in a number 28 stainless-steel hypodermic needle. The electrode was inserted in the cerebellum through a small hole drilled with a dental drill through the occipital bone above the nuchal ridge. The anode was a clip attached to a scalp muscle. The fastigial nucleus was stimulated with a 12 sec train of square wave pulses of 0·1 msec. duration at a stimulus frequency of 50 Hz, delivered to the animal from a pulse generator (Devices, Digitimer) through a stimulus isolation unit (Devices, MK IV). The stimulus current was measured by passing the output from the stimulator through a 10 Ω resistor and the voltage drop across this resistor was amplified by a Tektronics type 122 preamplifier and displayed on a cathode ray oscilloscope (Tektronics 360) where it was continuously monitored throughout the experiment. The pressor response was established as not due to spread of the stimulus current to the brainstem by previously defined criteria (Miura & Reis, 1969). These were the absence of facial twitching, a frequency maximum for the response between 30 and 80 Hz, and evidence at the end of the experiment that a punctate lesion placed at the electrode site abolished the evoked response.

After placement of the stimulating electrode the animal was paralysed with gallamine-triethiodide (5 mg/kg) and artificially ventilated by a Harvard respirator pump maintaining end-expired CO_2 at 2–3%. The threshold response was arbitrarily defined as a rise of the mean blood pressure greater than 10% of control. After establishing the threshold stimulus intensity the fastigial nucleus was stimulated at intensities of 1–5 times threshold, a range of stimulus intensities which does not result in a spread of the stimulus to the brainstem (Miura & Reis, 1970). In the usual experiment, after placement of a stimulating electrode and paralysing the animal, base line measurements of specific cardiovascular parameters were taken. After the animal had stabilized, a series of observations was taken before, during and after stimulation of the fastigial nucleus. The significance of changes in cardiovascular function was estimated by a paired *t* test (Snedecor & Cochran, 1967). At the termination of the experiment the stimulus site was marked by passage of a 20 μA current for 30 sec in order to deposit iron at the electrode tip.

D. Histological confirmation

At the termination of the experiment the animal was perfused with 10% formaldehyde and 1% potassium ferro- and ferricyanide in order to identify the position of the tips of the stimulating electrodes by the Prussian blue reaction (Crill & Reis, 1968). The brain was then fixed frozen and sectioned at 50 μ. The sites of iron deposition were identified before and after staining the sections for either cells (Nissl) or fibres (Weil).

RESULTS

A. Changes in arterial blood pressure and regional blood flow during the fastigial pressor response

As previously described (Miura & Reis, 1969, 1970, 1971; Achari & Downman, 1970; Lisander & Martner, 1971) electrical stimulation of the ventromedial portion of the rostral fastigial nucleus (fastigial pressor area) (Fig. 1) resulted in an elevation of systolic, diastolic and mean blood pressures (Table 1, Fig. 2). The pressure responses were graded (Fig. 2) and highly reproducible from cat to cat. Stimulation at 5 times the threshold increased the systolic blood pressure to 189% of control.

TABLE 1. Changes in cardiovascular dynamics associated with electrical stimulation of fastigial nucleus. Fastigial stimulation delivered with stimulus currents 5× threshold. All values expressed as mean ± S.E. of mean. n.s. = not significant

	N	Control	Fastigial stim.	Change (%)	*P*
		Systemic arterial pressure (mm Hg)			
Systolic pressure	29	130 ± 4	241 ± 6	+89	< 0·001
Diastolic pressure	29	99 ± 4	176 ± 4	+83	< 0·001
Mean pressure	29	110 ± 4	198 ± 4	+82	< 0·001
Pulse pressure	29	29 ± 2	64 ± 3	+141	< 0·001
		Venous pressure (cm H_2O)			
Central venous pressure	5	3·2 ± 0·7	3·6 ± 0·7	+13	n.s.
Occluded vein pressure	9	15·6 ± 0·9	17·0 ± 1·1	+8	n.s.
		Cardiodynamics			
Heart rate (beat/min)	29	223 ± 5	248 ± 5	+12	< 0·01
Cardiac output (ml./min)	11	422 ± 9	431 ± 10	+2	n.s.
Stroke volume (ml./beat)	11	1·83 ± 0·01	1·69 ± 0·03	+8	< 0·05
Cardiac contractile force (g)	4	31·8 ± 1·5	41·1 ± 1·4	+30	< 0·01
		Regional blood flow (ml./min)			
Femoral artery	29	11·7 ± 0·4	9·0 ± 0·5	−23	< 0·001
Axillary artery	10	10·7 ± 0·7	8·7 ± 1·0	−23	< 0·05
Renal artery	26	27·3 ± 0·7	13·6 ± 1·5	−48	< 0·001
Mesenteric artery	6	12·3 ± 1·0	8·6 ± 1·0	−26	< 0·05
Common carotid artery	9	17·8 ± 1·3	30·7 ± 2·5	+96	< 0·001
Ascending aorta	8	345 ± 6	339 ± 22	−1·6	n.s.
		Regional vascular resistance (mm Hg.min/ml.)			
Femoral artery	29	10·3 ± 0·5	24·0 ± 1·8	+132	< 0·001
Axillary artery	10	10·5 ± 0·6	26·2 ± 2·7	+159	< 0·001
Renal artery	26	3·7 ± 0·2	14·7 ± 2·3	+320	< 0·001
Mesenteric artery	6	9·5 ± 0·4	22·0 ± 2·8	+131	< 0·01
Common carotid artery	9	7·3 ± 0·7	6·6 ± 0·4	−6	n.s.
Ascending aorta	8	0·31 ± 0·03	0·58 ± 0·03	+91	< 0·01

Associated with the increase in blood pressure is a decrease in blood flow to the femoral, renal, axillary and mesenteric arteries. The decrease in flow is graded (Figs. 2, 3) and reflects an increase in vascular resistance (Table 1, Fig. 3). With the exception of renal blood flow, the changes in blood flow were sustained during the 12 sec stimulus. In the renal artery

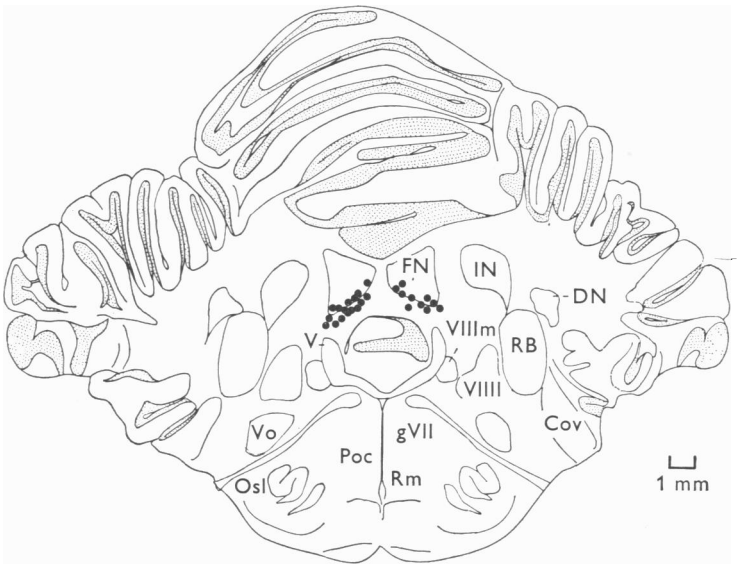

Fig. 1. Localization of sites in fastigial nucleus in twenty-six consecutive experiments from which a maximal pressor response was evoked in anaesthetized cats. The positive sites (filled circles) are displayed on a representative coronal cross-section of the brain stem at approximately the level of the rostral quarter of the nucleus. Abbreviations, according to Taber (1961): Cov, nucleus cochlearis dorsalis; DN, nucleus dentatus; FN, nucleus fastigii; gVII, genu nervi facialis; IN, nucleus interpositus; Osl, nucleus olivaris superior lateralis; Poc, nucleus pontis centralis caudalis; RB, corpus restiformis; Rm, nucleus raphe magnus; V, IV ventricle; Vo, nucleus tractus spinalis oralis; VIIII, nucleus vestibularis lateralis; VIIIm, nucleus vestibularis medialis.

the blood flow tended to drift back to control values during stimulation possibly as a consequence of renal autoregulation (Johansson, Sparks & Biber, 1970). A rebound overshoot of blood flow and a slowing of the heart rate often occurred after termination of the stimulus (Fig. 2).

The relative magnitude of changes in flow and resistance in different arteries is tabulated in Table 1. The greatest change occurred in the renal artery with vascular resistance increasing fourfold in contrast to the doubling of resistance in the femoral, axillary and mesenteric arteries. This greater responsiveness of the renal artery is also reflected in a stimulus response curve which is steeper than that of other vessels (Fig. 4).

Blood flow in the ascending aorta did not change during the fastigial pressor response (Fig. 5, Table 1) which, as described below, is an indication of an unchanged cardiac output during the response. However, the increase in resistance in the ascending aorta to 191 % of control indicates that the total peripheral resistance is almost doubled.

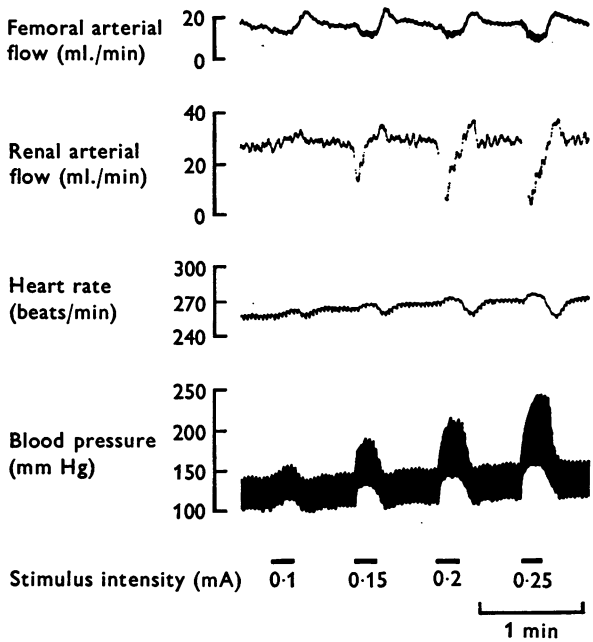

Fig. 2. Changes in femoral arterial blood flow (upper channel) renal arterial blood flow (second channel from top), heart rate (second channel from bottom) and aortic blood pressure (bottom channel) during graded electrical stimulation of the fastigial nucleus in a paralysed anaesthetized cat. The standard stimulus in this and subsequent illustrations consists of a 12-sec train of square-wave pulses of 0·1 msec duration delivered at 50 Hz (black bars at bottom of record). Stimulus intensity is enumerated in mA.

In several experiments blood flow was recorded simultaneously in both femoral or in both renal arteries. At no time was there any evidence of laterality of the response.

In contrast to the other vascular beds, blood flow in the common carotid artery increased during the fastigial pressor response (Table 1, Fig. 6). There are several lines of evidence suggesting that the increase in carotid blood flow reflects an increase in cerebral blood flow. First, the increased carotid flow persisted after removal of all muscles of the cranium, a large recipient of blood flow from the external carotid artery. Secondly, direct visualization of the pial vessels (exposed through a small hole placed in the calvarium and dura) through a dissecting microscope (at 12·5×

magnification) during the fastigial pressor response revealed a marked increase in arteriolar and venular flows and reddening of the cerebral veins.

The increased carotid blood flow during the fastigial pressor response was unassociated with any change in carotid arterial resistance (Fig. 7) and was of equal magnitude, when expressed as percent of control, to the elevation of blood pressure (being 96 % and 89 %, respectively; Table 1).

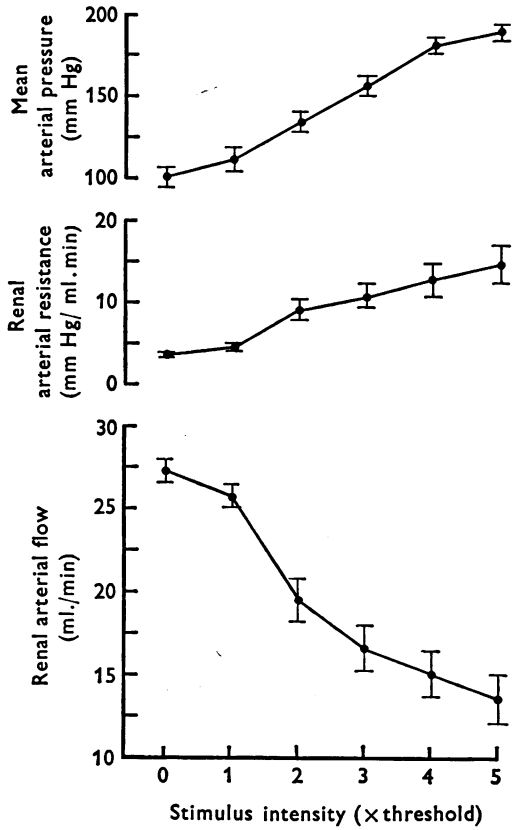

Fig. 3. Changes in mean arterial pressure (upper graph), renal arterial resistance (middle graph) and renal arterial blood flow (lower graph) during graded stimulation of the fastigial nucleus in anaesthetized paralysed cats. Each point represents mean ± S.E. of mean (n = 26).

This indicates that the change in cerebral blood flow is passive. This passive increase in flow during the fastigial pressor response is not found during hypertension produced by infusion of angiotensin II or norepinephrine. With pressor agents carotid arterial resistance increases due to autoregulation (Lassen, 1959; Sokoloff, 1949). The absence of resistance changes during the fastigial pressor response therefore suggests that autoregulation of the blood flow is suspended.

The vasoconstriction in the femoral, mesenteric, renal and axillary arteries as well as the hypertension were abolished by the systemic injection of the α-adrenergic blocking agent phentolamine (1 mg/kg I.V.) in four cats. This dose of the drug, however, did not alter the heart rate.

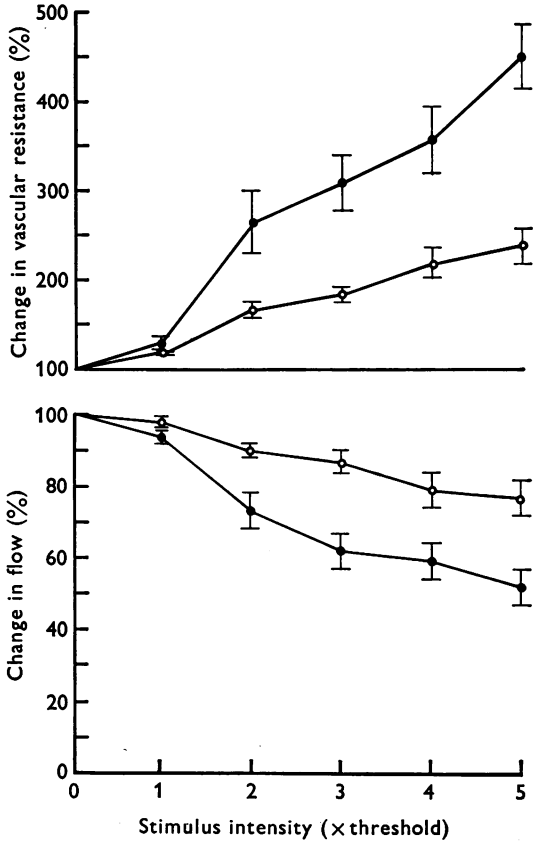

Fig. 4. Comparison of percentage change in arterial resistance (upper graph) and flow (lower graph) in renal (filled circles) and femoral (open circles) arteries during graded stimulation of the fastigial nucleus. Each point represents mean ± S.E. of mean (n = 26 for the renal artery and 29 for the femoral artery). Note the steep stimulus/response curve for renal arterial flow and resistance during the fastigial pressor response.

Surgical interruption of the renal (Fig. 8), femoral or sciatic nerves also reversed the local changes of flow from a decrease to an increase. Bilateral adrenalectomy did not affect the magnitude of the blood pressure or flow changes during the fastigial pressor response. The increase in peripheral vascular resistance during the fastigial pressor response therefore results from activity of post-ganglionic sympathetic neurones and is mediated by α-adrenergic receptors.

B. Changes in venous pressure

During the fastigial pressor response there were no changes in the central venous pressure (Table 1), nor in pressure measured in a distal segment of the femoral vein occluded proximally (occluded vein pressure). This contrasts with the increase in central venous pressure associated with the defence reaction evoked by hypothalamic stimulation in cat (Lisander 1970).

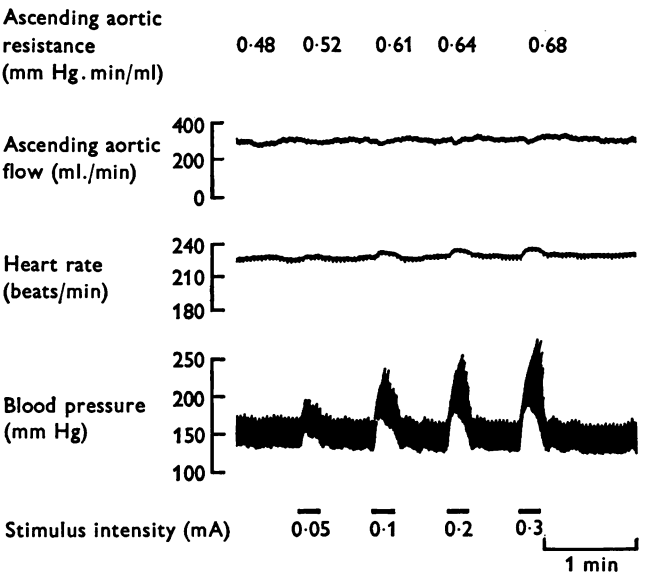

Fig. 5. Blood flow in ascending aorta (top channel), heart rate (middle channel), aortic blood pressure (bottom channel) and calculated resistance (numbers above aortic blood flow) during graded electrical stimulation of the fastigial pressor area in an anaesthetized paralysed cat. Note increase in resistance without significant change in aortic flow during fastigial stimulation.

C. Changes in cardiac function during the fastigial pressor response

During the fastigial pressor response there is a small but significant increase in the heart rate (Table 1, Figs. 2, 5, 8) sometimes associated with ventricular ectopic beats, and also an increase in myocardial contractile force (Fig. 9). Both changes in heart rate and contractility were abolished by transection of the cardiac nerves at the stellate ganglion (Fig. 9) or by intravenous injection of the β-adrenergic blocking drug propranolol (1 mg/kg I.V.). Thus the changes in heart rate and force evoked by stimulation of the fastigial nucleus were neurogenic and mediated by cardiac β-receptors.

Despite the increase in heart rate and myocardial contractile force the cardiac output was unchanged during the fastigial pressor response whether measured by ascending aortic flow (Fig. 5) or by the thermal dilution technique (Table 1). The unchanged cardiac output therefore must have resulted from a decrease in stroke volume (Table 1). The reduced stroke volume was presumably in turn the result of an increased afterload secondary to the augmented peripheral resistance (Kirchheim & Gross, 1971).

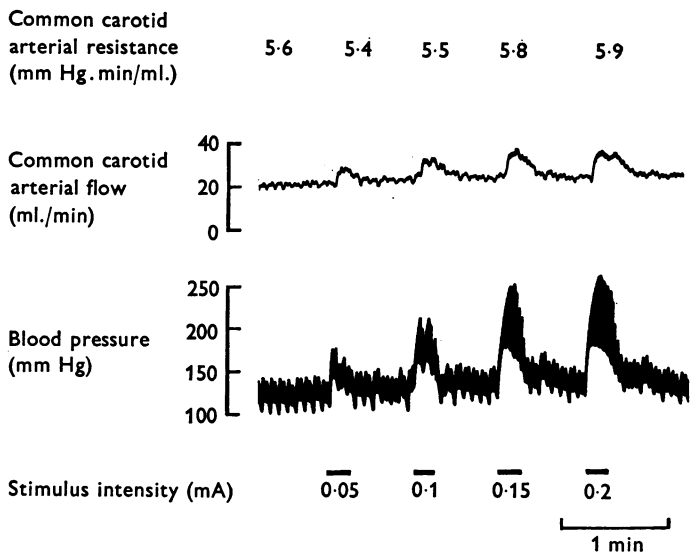

Fig. 6. Blood flow in common carotid artery (upper channel) aortic blood pressure (lower channel) and calculated resistance (above carotid flow channel) in the common carotid artery during graded stimulation of the fastigial pressor area in an anaesthetized paralysed cat. Note increase in flow without change in resistance during the fastigial pressor response.

D. Pupillary changes

There was minimal (less than 1·5 mm) dilatation or no change in pupillary diameter and no retraction of the nictitating membrane during the fastigial pressor response when elicited by electrical stimulation of 5 × threshold (Fig. 10). The absence of pupillary signs during the fastigial pressor response was not the result of inexcitability of the central peripheral pupillomotor pathways since stimulation of the postero-lateral hypothalamus in several experiments evoked, along with an elevation of blood pressure, a brisk bilateral retraction of the nictitating membrane and bilateral pupillary dilatation to 70–80 % of the maximum dilatation effected by stimulation of the distal end of the sympathetic nerve in the neck (Fig. 10).

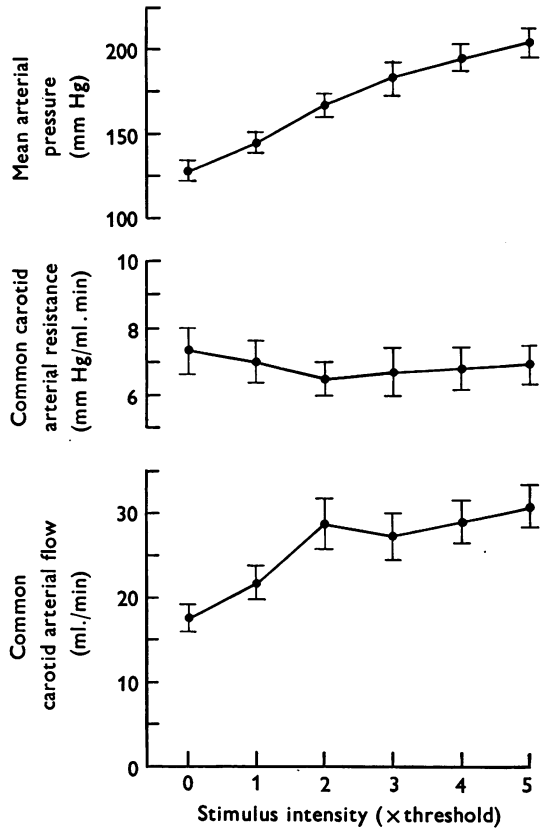

Fig. 7. Changes in mean arterial pressure (upper graph), common carotid arterial resistance (middle graph) and common carotid arterial blood flow (lower graph) during graded electrical stimulation of the fastigial pressor area in anaesthetized paralysed cats. Each point represents mean ± S.E. of mean (n = 9).

DISCUSSION

The present study indicates that stimulation of the rostral fastigial nucleus produces a complex, stereotyped and graded pattern of cardiovascular activity mediated by the sympathetic nervous system. The preponderant response to such stimulation is an alpha-adrenergically mediated constriction of the arteries to skeletal muscle (as evidenced by decreased flow in the femoral and axillary arteries), to kidney and to intestine. These findings are qualitatively in accord with the observations of Achari & Downman (1970) and Lisander & Martner (1971) who estimated blood flow by plethysmographic or drop recorder techniques respectively. As a consequence of the vasoconstriction there is a marked increase in the

peripheral vascular resistance resulting in an elevation of the systemic blood pressure.

Despite a β-adrenergically mediated increase in heart rate and myocardial contractility there is no change in the cardiac output. This is probably the consequence of the increased left ventricular afterload resulting from the increase in peripheral resistance thereby reducing the left ventricular stroke volume. This effect is similar to the mechanism responsible for the reduction in cardiac output induced by injection of vaso-active substances or by acute experimental hypertension (Olmsted & Page, 1965*a*, *b*).

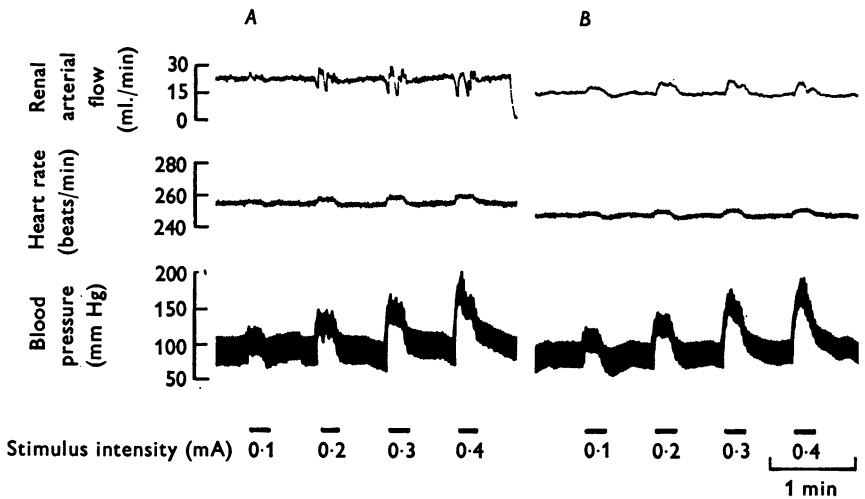

Fig. 8. Effects of transection of renal nerves on renal blood flow during the fastigial pressor response. Upper channel: renal arterial flow. Middle channel: heart rate. Lower channel: aortic blood pressure. *A*, before nerve transection. *B*, after nerve transection. Note reversal of blood flow from a reduction to an increase after nerve transection.

In addition to the direct activation of the sympathetic cardiovascular neurones there is simultaneously an inhibition of both the cardiovagal and the vasomotor components of the baroreceptor reflexes (Achari & Downman, 1970; Miura & Reis, 1971; Lisander & Martner, 1971). Such inhibition might serve, by blocking the bradycardia, to maintain the cardiac output in the face of the increased peripheral vasoconstriction.

The pattern of activation of the sympathetic neurons during the fastigial pressor response is differentiated, i.e. results from a selective rather than diffuse activation of sympathetic neurons. Thus, despite intense activation of sympathetic vasoconstrictor neurons supplying skeletal muscle, kidney and gut there is no sign of increased venoconstriction as reflected in the

central venous pressure or occluded vein pressure nor any change in the common carotid arterial resistance. Nor is there pupillary dilatation or retraction of the nictating membrane. These observations are in accord with recent evidence demonstrating that the sympathetic nervous system has a highly developed capacity to discharge selectively in an organ and function specific manner (e.g. Feigl, 1964; Hoffer, 1965; Clark, Smith & Shearn, 1968).

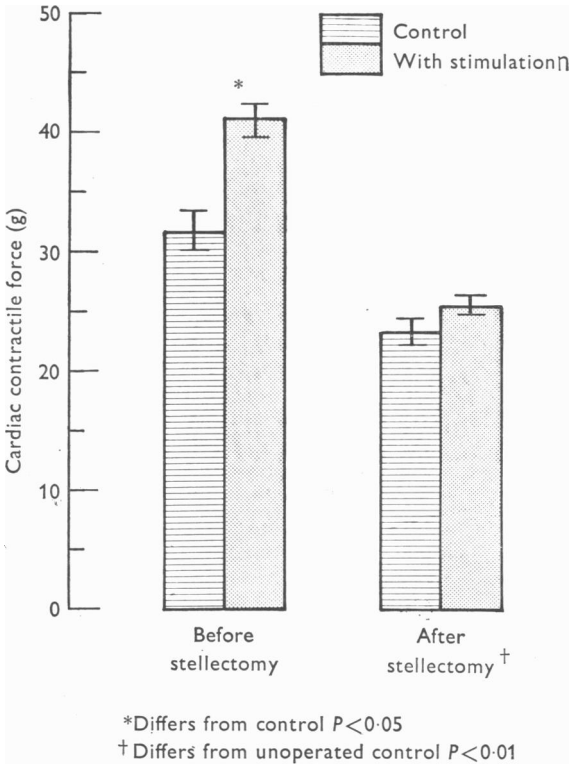

Fig. 9. Effects of stellate ganglionectomy on the increase in cardiac contractile force associated with the fastigial pressor response. Note that the increase in contractile force during fastigial stimulation (at 5 times threshold) is abolished by stellectomy. Stellate ablation also significantly reduces pre-stimulation myocardial contractility.

Although all the component parts characterizing the fastigial pressor response have been elicited alone or in partial combinations by brain stimulation (Feigl, 1964; Ueda, Inoue, Iizuka, Izuka Ihori & Yasuda, 1966), fastigial pressor response in its totality represents a patterned and stereotyped cardiovascular response unlike any heretofore evoked by electrical stimulation in brain or periphery. Its reproducibility and stereotopy are also distinctive. For example, it is unlike the defence reaction (Abrahams,

Hilton & Zbrozyna, 1960; Folkow *et al.* 1968; Lisander, 1970) or exercise responses (Smith, Rushmer & Lasher, 1960) in which an elevated blood pressure and tachycardia are associated with increased flow to muscle and an increase in the cardiac output. It also differs from peripherally or centrally induced reflex responses to hypoxia (Downing, Remensnyder & Mitchell, 1962; Daly & Scott, 1963; Downing, Mitchell & Wallace, 1963;

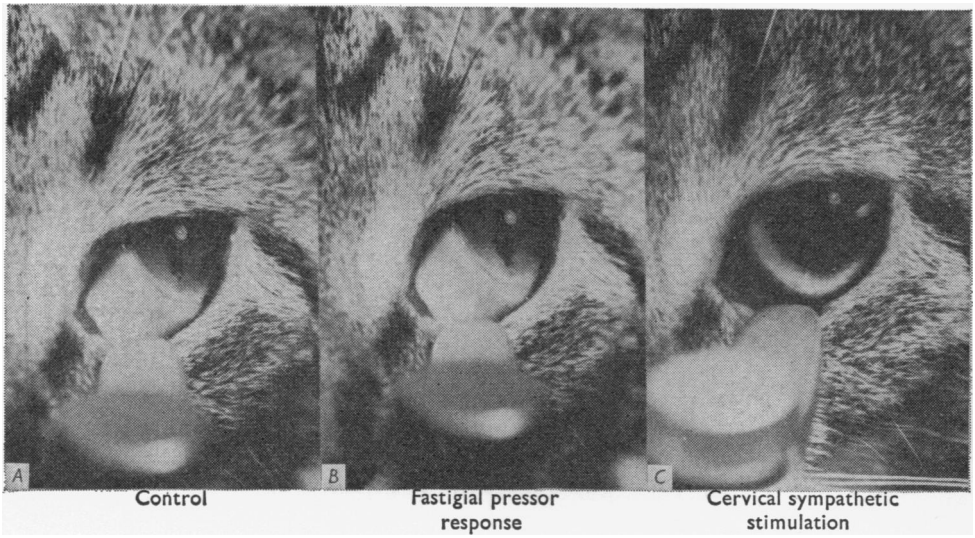

Fig. 10. Absence of pupillary dilatation or retraction of nictitating membrane during the fastigial pressor response. *A*, control. *B*, during the fastigial pressor response at 5 times threshold. *C*, electrical stimulation of vago-sympathetic nerve. The cut distal end of the nerve was placed on a bipolar electrode and stimulated with an electrical stimulus pulse train of square wave pulses of 0·1 msec duration delivered at 50 Hz supramaximal for pupillary dilatation.

Daly, Hazzledine & Howe, 1965; Reis & McHugh, 1968) and diving responses (Feigl & Folkow, 1963; Yonce & Folkow, 1970) in which vasoconstriction in limb and visceral beds is associated with a bradycardia. However, comparison with other cardiovascular responses in which vasoconstriction and tachycardia are prominent reveals that the fastigial pressor response closely resembles the integrated cardiovascular response to maintenance of an upright posture (the orthostatic reflexes). It also, in large measure, simulates the differentiated response to carotid sinus hypotension or occlusion (Lisander & Martner, 1971) which is believed to be the principal stimulus to the orthostatic reflexes (Gauer & Thron, 1965).

We would therefore propose that the cardiovascular responses associated with the fastigial pressor response result from excitation of the neural networks which subserve the orthostatic reflexes. Further support for this

contention is our finding that small lesions within the bilateral fastigial pressor areas but not elsewhere in the cerebellum will impair the compensatory cardiovascular responses to headup tilting in the paralysed anaesthetized cat (Doba & Reis, 1972*a*, *b*).

That the fastigial nucleus is involved in postural cardiovascular reflexes is not surprising in view of its critical participation in somatic postural responses. Moreover the rostral fastigial nucleus receives a projection from the anterior mid line vermis (Jansen & Brodal, 1940) the only portion of the cerebellar vermis from which cardiovascular changes have been consistently elicited by electrical stimulation (Hoffer, 1965). Stimulation of the anterior vermis produces, in general, increased flows to skeletal muscle due to sympathetic inhibition often associated with decreased renal flow, a pattern more appropriate to the defence reaction or exercise than to postural responses. This raises the interesting possibility that the Purkinje cells of the anteromedial cerebellar cortex may produce phasic increases in muscle flow in relationship to movement by inhibiting neurons of the fastigial nucleus (Eccles, Ito & Szentogothai, 1967; Ito, Yoshida, Obata, Kawai & Udo, 1970). The role of the fastigial nucleus in autonomic postural reflexes postulated here would serve as another demonstration of the intimate functional coupling between the somatic and autonomic motor system in the brain.

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