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# CARDIOVASCULAR RESPONSES EVOKED FROM THE FASTIGIAL REGION OF THE CEREBELLUM IN ANAESTHETIZED AND DECEREBRATE RABBITS

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SUMMARY

1. The rostral and caudal regions of the fastigial nucleus (f.n.) in both anaesthetized and decerebrate rabbits have been stimulated electrically while monitoring phrenic nerve activity, heart rate, blood pressure and blood flow to the kidney and hindlimb in addition to recording renal sympathetic nerve activity.

2. Stimulation of the rostral region of the f.n. in the anaesthetized and decerebrate rabbit produced a silencing of phrenic nerve discharge, either no change in heart rate or a vagally mediated bradycardia and a pressor response associated with vasoconstriction in both renal and femoral beds which resulted from an increase in sympathetic vasomotor tone.

3. Stimulation of the caudal region of the f.n. in the anaesthetized rabbit evoked apnoea and a bradycardia which was partially attenuated by vagal blockade. Also, a depressor response was obtained with no change in renal vascular resistance, a transient inhibition of renal sympathetic nerve discharge and a vasodilation in the hindlimb resulting from the withdrawal of sympathetic vasoconstrictor tone. In contrast, electrical stimulation of the same site in the unanaesthetized decerebrate rabbit evoked an increase in central inspiratory drive, a tachycardia and a pressor response with vasoconstriction in both vascular beds. The cardiac and vascular responses were abolished after sympathetic blockade.

4. Administration of a small dose of anaesthetic to the decerebrate preparation did not affect the direction of the cardiovascular or central respiratory responses evoked from the rostral f.n. but reversed the pattern of response elicited from the caudal f.n. to that seen in the intact anaesthetized rabbit.

5. The results of the present study suggest the existence of two separate regions associated with the f.n. which can influence the cardiovascular system in the rabbit. Furthermore, it would seem that the cardiovascular responses evoked from the vicinity of the caudal and rostral poles of the f.n. are mediated by two distinct pathways which might suggest two separate functional roles for the cerebellum in cardiovascular control in the rabbit.

## INTRODUCTION

As part of an ongoing study into the role of the cerebellum in cardiovascular control we have recently described the heart rate, blood pressure and regional blood flow changes which can be elicited by stimulation of a localized region of the posterior cerebellar cortex, the uvula or Larsell's lobule IX. The cardiovascular pattern of response evoked either electrically (Bradley, Ghelarducci, Paton & Spyer, 1987*a*) or chemically (Bradley, Ghelarducci, Paton & Spyer, 1987*b*) in the anaesthetized animal is qualitatively opposite to the response elicited from an equivalent region in the unanaesthetized decerebrate preparation.

To date there is limited information concerning the role of the caudal fastigial nucleus (f.n.) and particularly its influence on the cardiovascular system in any species. However, a recent report has indicated a pressor site in the caudal and a second in the rostral division of the f.n. in the anaesthetized rabbit (Nisimaru & Kawaguchi, 1984). It is well established that in many species a pressor response can be evoked by stimulation of the rostral f.n. (the conscious dog, Dormer & Stone, 1976*b*; the anaesthetized dog, Dormer & Stone, 1976*a*; the conscious cat, Achari, Al-Ubaidy & Downman, 1973; the anaesthetized cat, Achari & Downman, 1970, and Doba & Reis, 1972; and the anaesthetized rat, Chida, Iadecola, Underwood & Reis, 1986); and this is usually associated with tachycardia.

In the present study we have stimulated electrically throughout the entire f.n. region and the adjacent white matter to determine in detail the pattern of cardiovascular response that can be evoked from this area of the cerebellum. Particular attention has been paid to the caudal f.n. since previously obtained anatomical data showed this region to contain a large number of the efferent fibres descending from the uvula (Barrett, Bradley, Paton & Spyer, 1985). Since the direction of the cardiovascular responses elicited from the uvula is anaesthetic sensitive, we have compared the responses obtained in the anaesthetized and unanaesthetized decerebrate rabbit.

A preliminary report of part of this work has been published in abstract form (Bradley, Paton & Spyer, 1986).

## METHODS

A total of thirty-two New Zealand White rabbits (2·0–3·2 kg) were used in this study and of these eleven were anaesthetized with urethane (Sigma Ltd, U.K., 1·4 g $kg^{-1}$ given I.V.) and twenty-one were anaesthetized with alphaxalone alphadolone (Saffan, Glaxovet Ltd, U.K., 3 mg $kg^{-1}$ given I.V., and supplemented with 3 mg bolus injections as required). The right jugular vein was cannulated to allow injections of anaesthetic and drugs. The trachea was intubated below the larynx and the bladder cannulated and drained in all animals. End-tidal $CO_2$ was monitored continuously using an infra-red gas analyser (P. K. Morgan Ltd, U.K., model 901) and maintained at $4·5 \pm 0·5$ %. Blood gas analysis was carried out at regular intervals throughout each experiment using a blood gas analyser (Corning Medical & Scientific, U.S.A., model 158). Blood arterial oxygen pressure ($P_{a,O_2}$), pH, arterial carbon dioxide pressure ($P_{a,CO_2}$) and $HCO_3^-$ levels were noted and, if necessary, corrected by appropriate infusions or altering minute volume and/or inspired gas composition. In some animals the right femoral artery was cannulated and in others the right common carotid artery was cannulated and connected to a transducer (Gould Statham, U.S.A., P23Db) for measurement of arterial blood pressure, heart rate being derived from the pulse waveform by a rate-meter (Neurolog, Digitimer Ltd, U.K., model NL250). Rectal temperature was maintained at $38 \pm 0·5$ °C using a heating lamp.

The rabbits anaesthetized with Saffan and two of the animals anaesthetized with urethane were paralysed but only after the depth of anaesthesia had been fully assessed by observing the withdrawal reflex to pinching of a paw. In seventeen rabbits gallamine triethiodide (Flaxedil, May & Baker Ltd, U.K., 4 mg $kg^{-1}$) was injected I.V. and in four animals decamethonium bromide (Sigma Ltd, U.K., 0·25 mg $kg^{-1}$ I.V. and supplemented as required) was used because of its non-vagolytic properties, so that the neural mechanisms involved in the cardiac responses could be examined subsequently. These animals were ventilated artificially (Harvard Apparatus Co., U.S.A., model 665) with air enriched with oxygen and a tidal volume of 12–18 ml was used at 45–65 cycles $min^{-1}$ such that blood acid–base status was kept within control limits. Once both common carotid arteries were ligated, the animals anaesthetized with Saffan were decerebrated using suction and undercutting techniques leaving the superior colliculi intact.

In all animals the posterior cerebellar vermis was exposed by dissection and retraction of the nuchal muscles and the overlying occipital bone and dura were removed. The fastigial nuclei were located according to the co-ordinates of Brodal (1940), and were approximately 1·5 mm lateral to obex. Stimulation was via a monopolar metal filled microelectrode, tip diameter 15–35 $\mu$m, with a 6 s pulse train (0·2 ms, 100 Hz) of cathodal current which was displayed on an oscilloscope (Tektronix U.K., Ltd, model 5110). The electrode was held in a micro-manipulator (Narishige, Japan, model 2168) and lowered into the cerebellum through sub-lobule a of the uvula. Once within the nucleus, the electrode was advanced in 0·25 mm steps and the f.n. stimulated to a depth of 6·25–7·5 mm below the cerebellar surface. In the anaesthetized rabbits currents effective in evoking cardiovascular responses were in the range 150–350 $\mu$A whilst 50–200 $\mu$A was effective in decerebrate animals.

Blood flows to the kidney and hindlimb were monitored simultaneously with electromagnetic flowmeters (Carolina Medical Electronics Inc., U.S.A.) and changes in renal sympathetic nerve activity were recorded as previously reported by us (Bradley *et al.* 1987*a*). In six animals the right phrenic nerve was isolated and a record of central inspiratory activity was obtained using a bipolar silver wire hook electrode. In these animals a side arm of the tracheal cannula was connected to a transducer (Gould Statham, U.S.A., P23Db) for measurement of tracheal pressure. The right cervical vagus was stimulated with a bipolar silver wire electrode in two animals using a 1–2 s pulse train (0·5 ms, 20 Hz, 5–10 V), before and after administration of atropine, so that the effectiveness of the drug could be assessed. Three decerebrate rabbits were effectively de-buffered by sectioning both aortic nerves, previously identified by the characteristic rhythm of the recorded afferent activity, and by occluding both common carotid arteries.

In some experiments one-eighth the full anaesthetic dose of either urethane (190 mg $kg^{-1}$ Sigma Ltd, U.K.), $\alpha$-chloralose (10 mg $kg^{-1}$ BDH Chemicals Ltd, U.K.) or sodium pentobarbitone (5 mg $kg^{-1}$, May & Baker Ltd, U.K.) was administered I.V. to the decerebrate rabbits to observe the effects of anaesthesia on the evoked responses.

The final position of the stimulating electrode was marked by an electrolytic lesion made by passing 50 $\mu$A constant current for 30 s. The lesion and electrode track, together with the level of decerebration in the decerebrated animals was identified by cutting sagittal sections (80–100 $\mu$m), which were stained, cleared and mounted using standard histological techniques. In each case decerebration was shown to result in the removal of the hypothalamus.

All variables except renal sympathetic nerve activity were recorded on an eight-channel recorder (Gould Electronics, U.S.A., model 2800S), and from this the peak responses analysed using Minitab statistical package (two-sample *t* test) on a PDP 11/34 computer.

*Drugs used.* Atenolol hydrochloride (ICI, Plc, U.K.); atropine sulphate (Sigma Ltd, U.K.); guanethidine monosulphate ('Isemelin', Ciba Labs Ltd, U.K.); isoprenaline hydrochloride ('Saventrine', Pharmax Ltd, U.K.); noradrenaline acid tartrate ('Levophed', Winthrop Labs Ltd, U.K.); phenylephrine hydrochloride (Sigma Ltd, U.K.). All drugs were dissolved in 0·9 % saline and administered I.V.

## RESULTS

The results are based on two groups of data derived from experiments with stimulation sites in the vicinity of the caudal or rostral regions of the f.n. as identified histologically. Typically effective points of stimulation were restricted to areas 3·75–4·5 mm ('caudal f.n.') and 5·5–7·25 mm ('rostral f.n.') beneath the cortical

surface. When the area between these two regions of the f.n. was stimulated either no changes or very small and inconsistent cardiovascular responses were evoked. The data quoted are the changes in heart rate, mean arterial blood pressure, renal and femoral vascular conductance, the control values are given in Tables 1 and 2.

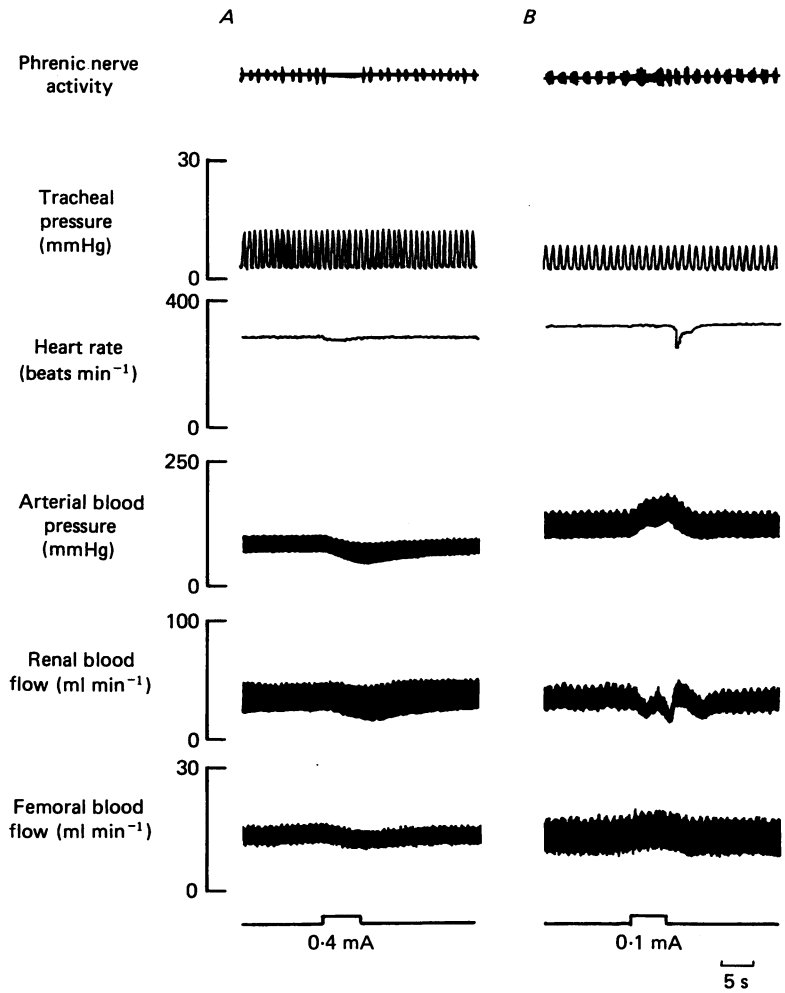


Fig. 1. Comparison of the cardiovascular and central respiratory changes in the anaesthetized rabbit during electrical stimulation in the caudal (*A*) and rostral (*B*) regions of the f.n.

*Responses in anaesthetized rabbits* ($n = 11$)

Stimulation of both the caudal and rostral regions of the f.n. in nine spontaneously breathing animals failed to elicit any overt somatic movements ($n$ refers to the number of animals and $t$ to the number of tests).

*Rostral f.n.* Electrical stimulation of the rostral f.n. in four animals evoked either no measurable change in heart rate ($t = 12$, Fig. 1*B*) or in five rabbits a significant bradycardia of $23{\cdot}8 \pm 1{\cdot}19$ beats min$^{-1}$ ($P < 0{\cdot}01$; $t = 17$, Table 1). The heart rate

TABLE 1. A comparison of the changes (mean ± S.E. of mean) and control values for heart rate, arterial blood pressure, renal vascular conductance and femoral vascular conductance during rostral f.n. stimulation in the anaesthetized, unanaesthetized decerebrate and anaesthetized decerebrate preparations. The directional changes in renal sympathetic nerve activity and phrenic nerve activity are also indicated. ($n$ = number of animals, + indicates an increase and − a decrease in the response)

| | Anaesthetized ($n = 11$) | | Decerebrate ($n = 15$) | | Anaesthetized decerebrate ($n = 9$) | |
|---|---|---|---|---|---|---|
| | Control | Response | Control | Response | Control | Response |
| Heart rate (beats $min^{-1}$) | 303 ± 5 | −24 ± 3 | 266 ± 6 | −67 ± 6 | 290 ± 10 | −33 ± 7 |
| Mean arterial blood pressure (mmHg) | 83 ± 2 | +27 ± 1 | 105 ± 2 | +36 ± 2 | 74 ± 4 | +41 ± 5 |
| Renal conductance (ml $min^{-1}$ $mmHg^{-1}$) | 0·39 ± 0·03 | −0·16 ± 0·02 | 0·30 ± 0·02 | −0·21 ± 0·02 | 0·38 ± 0·03 | −0·24 ± 0·02 |
| Femoral conductance (ml $min^{-1}$ $mmHg^{-1}$) | 0·13 ± 0·02 | −0·04 ± 0·01 | 0·11 ± 0·01 | −0·04 ± 0·01 | 0·19 ± 0·02 | −0·04 ± 0·01 |
| Renal sympathetic nerve activity | | ↑ | | ↑ | | ↑ |
| Phrenic nerve activity | | ↓ | | ↓ | | ↓ |

changes have only been analysed if the onset of the bradycardia preceded any change in mean arterial pressure. Any decreases in heart rate following the stimulus period have been attributed to reflex inputs and are not included in the analysis (see for example Fig. 1*B*). In some animals arrhythmias were evoked especially using the higher stimulus currents. In all nine animals there was a pressor response of 27·2 $\pm$1·34 mmHg ($t = 29$, Table 1, Fig. 1*B*) which was accompanied by a significant decrease in renal blood flow in four rabbits. The decrease of 8·15$\pm$1·8 ml min$^{-1}$ from a basal value of 32·5$\pm$2·61 ml min$^{-1}$ ($P < 0{\cdot}01$; $t = 13$) indicated that renal conductance had decreased significantly by 0·163$\pm$0·016 ml min$^{-1}$ mmHg$^{-1}$ ($P < 0{\cdot}01$; $t = 13$, Table 1). The change in vascular resistance was shown in two animals to result from a marked increase in renal sympathetic nerve discharge ($t = 8$, Fig. 2*A*). This increase in efferent activity was maintained throughout the period of stimulation but was followed by a post-stimulus inhibition lasting until arterial pressure had reached control levels.

Hindlimb blood flow in two rabbits remained unchanged, or showed a small and insignificant increase ($P > 0{\cdot}33$, $t = 6$, Fig. 1*B*), during rostral f.n. stimulation. Femoral vascular conductance, however, decreased significantly by 0·038$\pm$0·01 ml min$^{-1}$ mmHg$^{-1}$ ($P < 0{\cdot}02$; $t = 6$, Table 1), indicating vasoconstriction in this vascular bed. Excitation within the vicinity of the rostral f.n. in four rabbits either decreased the rate of central respiratory activity (Fig. 1*B*) or produced apnoea as judged by the effect on phrenic nerve activity.

*Caudal f.n.* Stimulation of the caudal f.n. in eight animals evoked a bradycardia of 19·2$\pm$2·7 beats min$^{-1}$ ($P < 0{\cdot}01$; $t = 25$, Table 2) and a depressor response of 23·0$\pm$1·04 mmHg ($t = 25$, Fig. 1*A*, Table 2). In three animals renal blood flow decreased significantly by 5·3$\pm$1·0 ml min$^{-1}$ from a control value of 33·7$\pm$4·2 ml min$^{-1}$ ($P < 0{\cdot}01$; $t = 8$, Fig. 1*A*), but there was no significant change in vascular conductance ($P > 0{\cdot}07$; $t = 8$). In addition, there was only a transient inhibition of renal sympathetic nerve activity during caudal f.n. stimulation (Fig. 3*A*). In contrast, femoral blood flow showed a small, yet significant, fall of 1·9$\pm$0·75 ml min$^{-1}$ from a control of 13·5$\pm$1·25 ml min$^{-1}$ ($P < 0{\cdot}05$; $t = 8$, Fig. 1*A*) but a significant increase in calculated vascular conductance of 0·03$\pm$0·01 ml min$^{-1}$ mmHg$^{-1}$ ($P < 0{\cdot}02$, $t = 8$, Table 2), indicating vasodilatation. In four animals where phrenic nerve activity was recorded, stimulation of the caudal f.n. region resulted in apnoea.

Electrical stimulation of both rostral and caudal regions of the f.n. in two anaesthetized rabbits which were paralysed and ventilated artificially evoked qualitatively similar responses to those detailed for the animals breathing spontaneously. In both cases no measurable change in heart rate was recorded. In addition, the cardiovascular changes elicited from the f.n. were found not to be secondary to changes in central respiratory activity, since hyperventilation or hypoventilation, caused by adjusting the minute volume, abolished the phrenic response to f.n. stimulation but had no effect on the evoked cardiovascular responses.

*Responses in decerebrate rabbits ($n = 21$)*

*Rostral f.n.* The cardiovascular responses evoked from the rostral f.n. in the decerebrate rabbit were qualitatively identical but quantitatively more marked than those evoked from similar regions of the nucleus in the anaesthetized animal. In

fifteen animals when the rostral f.n. was stimulated a bradycardia of $66{\cdot}6 \pm 5{\cdot}7$ beats $min^{-1}$ was elicited whose onset preceded any change in arterial pressure, together with a pressor response of $35{\cdot}9 \pm 1{\cdot}6$ mmHg ($t = 52$, Table 1, Fig. 4*B*). In five animals arrhythmias could be initiated with the higher stimulating currents. In ten animals where both renal and femoral blood flows were monitored the increase

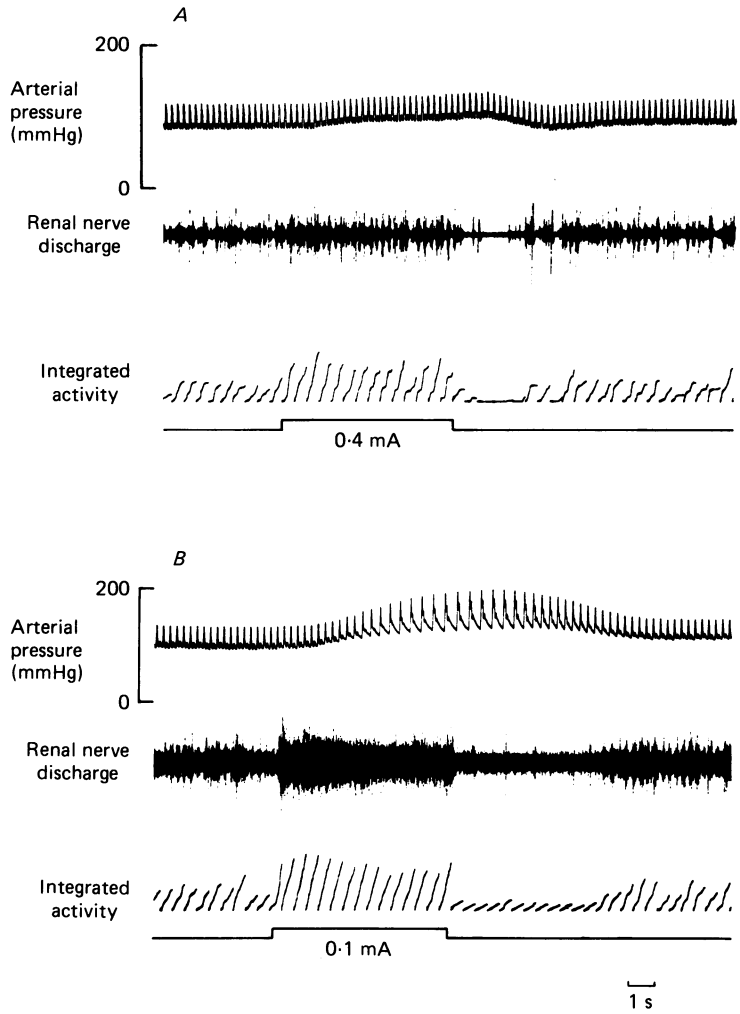


Fig. 2. Comparison of changes in arterial blood pressure, renal nerve discharge and its integrated activity during stimulation of the rostral f.n. in the anaesthetized (*A*) and decerebrate (*B*) rabbit.

in arterial pressure was associated with a significant fall in renal blood flow of $18{\cdot}2 \pm 1{\cdot}56$ ml $min^{-1}$ from a control of $29{\cdot}6 \pm 1{\cdot}4$ ml $min^{-1}$ ($P < 0{\cdot}01$; $t = 40$). This resulted in a significant decrease in renal conductance of $0{\cdot}214 \pm 0{\cdot}02$ ml $min^{-1}$ $mmHg^{-1}$ ($P < 0{\cdot}01$; $t = 40$, Table 1) indicative of vasoconstriction, a suggestion supported by the large maintained increase in renal sympathetic nerve activity observed in three rabbits ($t = 12$, Fig. 2*B*). There usually followed a post-stimulus

TABLE 2. A comparison of the cardiovascular and respiratory changes (mean ± S.E. of mean) and control values during caudal f.n. stimulation in the anaesthetized, unanaesthetized decerebrate and anaesthetized decerebrate rabbit. ($n$ = number of animals, + indicates an increase and − a decrease in the response. *Values not significant at the 5% level)

| | Anaesthetized ($n = 11$) | | Decerebrate ($n = 17$) | | Anaesthetized decerebrate ($n = 9$) | |
|---|---|---|---|---|---|---|
| | Control | Response | Control | Response | Control | Response |
| Heart rate (beats $min^{-1}$) | 318 ± 6 | −19 ± 3 | 260 ± 6 | +41 ± 3 | 306 ± 9 | −13 ± 3 |
| Mean arterial blood pressure (mmHg) | 81 ± 1 | −23 ± 1 | 105 ± 2 | +44 ± 3 | 84 ± 3 | −20 ± 2 |
| Renal conductance (ml $min^{-1}$ $mmHg^{-1}$) | 0·40 ± 0·04 | +0·05 ± 0·02* | 0·28 ± 0·02 | −0·20 ± 0·02 | 0·36 ± 0·03 | +0·01 ± 0·02* |
| Femoral conductance (ml $min^{-1}$ $mmHg^{-1}$) | 0·16 ± 0·02 | +0·03 ± 0·01 | 0·11 ± 0·01 | −0·04 ± 0·01 | 0·15 ± 0·01 | +0·03 ± 0·01 |
| Renal sympathetic nerve activity | | ↓ | | ↑ | | ↓ |
| Phrenic nerve activity | | ↓ | | ↑ | | ↓ |

inhibition of discharge until arterial pressure had returned to control levels. Likewise stimulation of the rostral f.n. elicited a small, but significant, fall in femoral blood flow of $1{\cdot}53 \pm 0{\cdot}44$ ml min$^{-1}$ from a resting level of $11{\cdot}5 \pm 0{\cdot}5$ ml min$^{-1}$ ($P < 0{\cdot}01$; $t = 40$) and a significant decrease in femoral conductance of $0{\cdot}04 \pm 0{\cdot}006$ ml min$^{-1}$

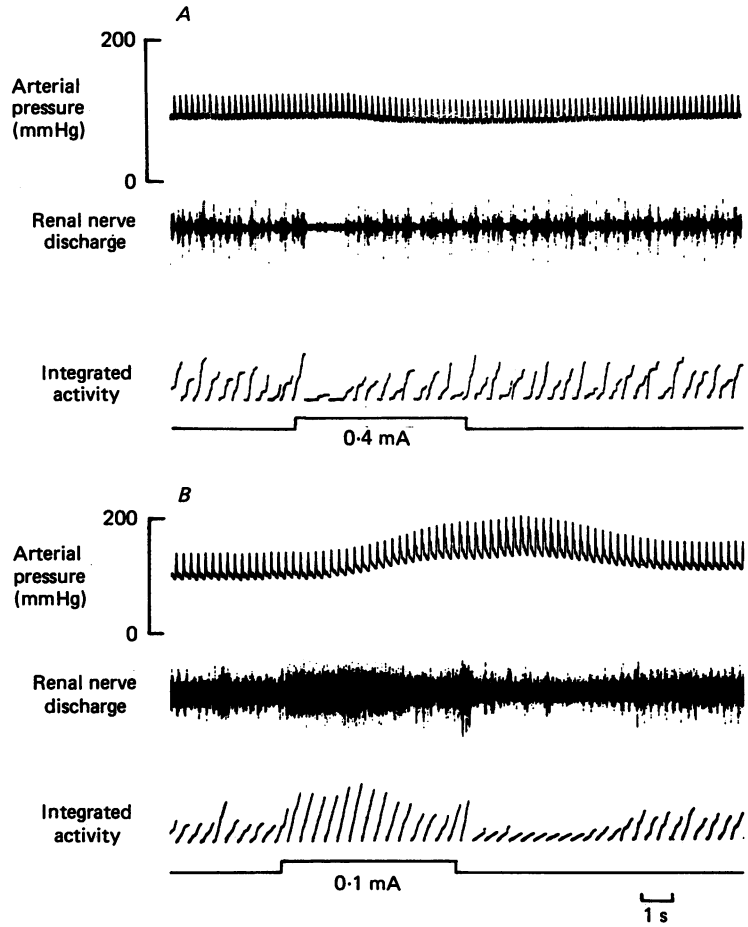


Fig. 3. Comparison of changes in arterial blood pressure, renal nerve discharge and its integrated activity during stimulation of the caudal f.n. in the anaesthetized (*A*) and decerebrate (*B*) rabbit.

mmHg$^{-1}$ ($P < 0{\cdot}01$; $t = 40$, Table 1). Central respiratory activity was silenced in four decerebrate rabbits (Fig. 4*B*) and the rate and amplitude attenuated in a further three animals during stimulation in the vicinity of the rostral f.n.

*Caudal f.n.* In seventeen decerebrate rabbits stimulation of the caudal regions of the f.n. evoked a tachycardia of $41{\cdot}3 \pm 3{\cdot}1$ beats min$^{-1}$ and a pressor response of $43{\cdot}8 \pm 3{\cdot}0$ mmHg usually followed by a post-stimulus bradycardia ($t = 24$, Table 2, Fig. 4*A*). Pulse pressure also increased as arterial pressure returned to baseline levels. In ten of these rabbits blood flow was monitored and the increase in arterial pressure was accompanied by a significant fall in renal blood flow of $17{\cdot}2 \pm 2{\cdot}3$ ml min$^{-1}$ from

a control of $28{\cdot}1 \pm 1{\cdot}5$ ml $min^{-1}$ ($P < 0{\cdot}01$; $t = 24$, Fig. 4*A*). Renal conductance showed a significant decrease of $0{\cdot}2 \pm 0{\cdot}02$ ml $min^{-1}$ $mmHg^{-1}$ ($P < 0{\cdot}01$; $t = 24$, Table 2), which in addition to the increase in renal sympathetic nerve discharge observed (Fig. 3*B*), indicated vasoconstriction in this vascular bed. In comparison there were variable and small changes in femoral blood flow which were not significant ($P >$

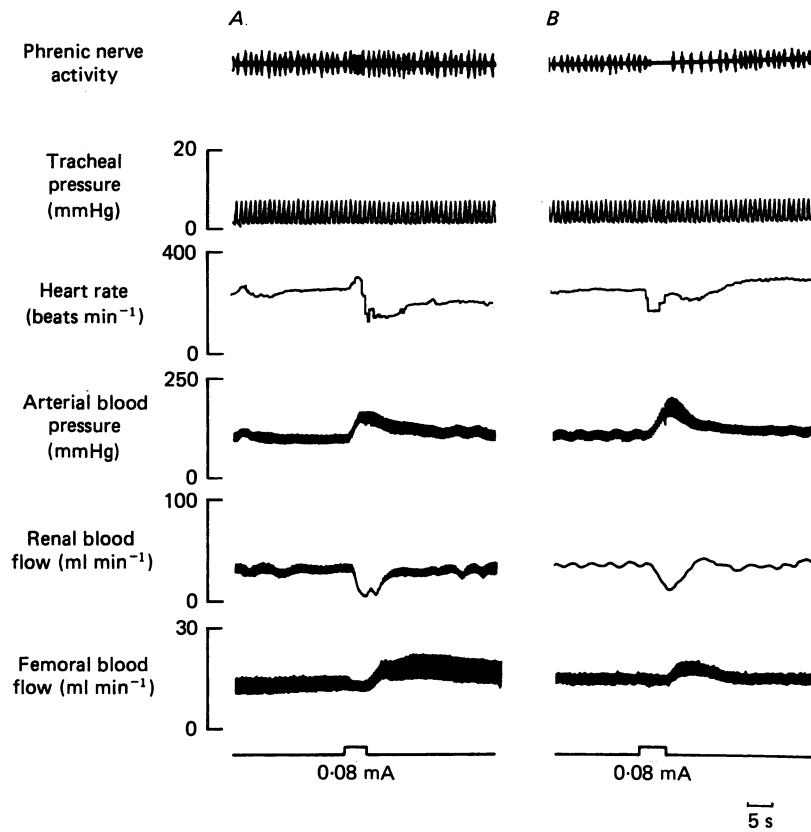


Fig. 4. Comparison of the cardiovascular and central respiratory responses in the decerebrate rabbit during stimulation of the caudal (*A*) and rostral (*B*) areas of the f.n.

0·94) during stimulation within the caudal f.n. These were usually followed by a long-lasting increase in flow that began with the cessation of the stimulus. Femoral conductance during the stimulus period decreased significantly by $0{\cdot}04 \pm 0{\cdot}006$ ml $min^{-1}$ $mmHg^{-1}$ ($P < 0{\cdot}01$) suggesting vasoconstriction in this vascular bed (Table 2). In all animals phrenic nerve activity was augmented (Fig. 4*A*) by stimulating in the caudal f.n. area, often resulting in apneustic discharge. The cardiovascular effects elicited from the caudal f.n. region were not secondary to the changes in central respiratory activity since hyper- or hypoventilation of the animal had no qualitative effects on the evoked pattern of response.

*Responses in anaesthetized decerebrate rabbits* ($n = 9$)

In nine of the eighteen decerebrate animals one-eighth of the full anaesthetic dose (either urethane, α-chloralose or sodium pentobarbitone, see Methods) was admin-

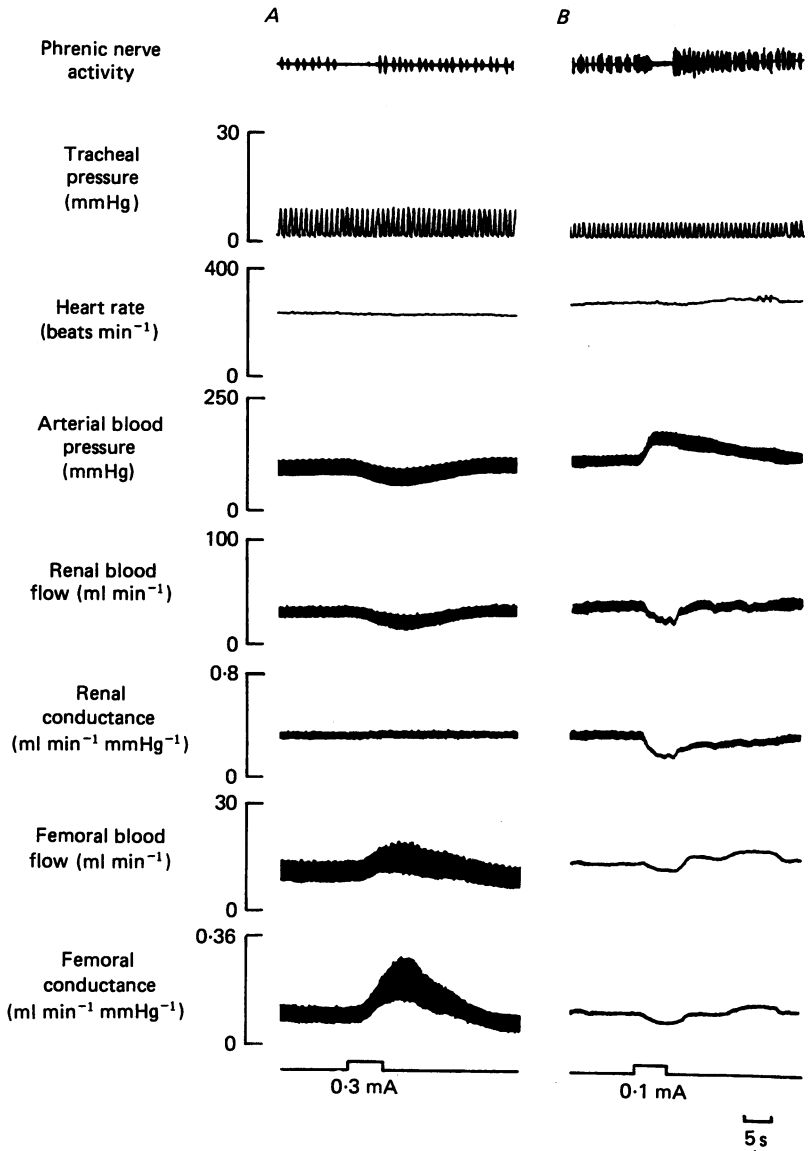


Fig. 5. Comparison of cardiovascular and central respiratory changes elicited from the anaesthetized decerebrate rabbit (sodium pentobarbitone 5 mg $kg^{-1}$ I.V.) during stimulation of the caudal (*A*) and rostral (*B*) regions of the f.n.

istered. Stimulation of the caudal and rostral regions of the f.n. then evoked cardiovascular patterns of response that were qualitatively similar to those described for the 'intact' anaesthetized animals.

*Rostral f.n.* Stimulation within the rostral f.n. evoked no change in heart rate ($n = 4$) or a bradycardia ($n = 5$) of $33{\cdot}1 \pm 7{\cdot}3$ beats $min^{-1}$ which occurred before any change in arterial pressure, and a pressor response of $41{\cdot}2 \pm 4{\cdot}9$ mmHg (Table 1, Fig. 5*B*). The increase in arterial pressure was associated with a significant fall in renal

blood flow of $14{\cdot}0 \pm 2{\cdot}5$ ml $min^{-1}$ from a control of $29{\cdot}3 \pm 1{\cdot}5$ ml $min^{-1}$ ($P < 0{\cdot}01$; $t = 10$), as a result renal conductance was shown to decrease by $0{\cdot}24 \pm 0{\cdot}02$ ml $min^{-1}$ $mmHg^{-1}$ ($P < 0{\cdot}01$; $t = 10$, Table 1). The marked increase in renal nerve activity also suggested vasoconstriction in this vascular bed during rostral f.n. stimulation. In addition, femoral blood flow showed no significant change ($P > 0{\cdot}07$; $t = 10$, Fig. 5*B*) but vascular conductance decreased by $0{\cdot}04 \pm 0{\cdot}007$ ml $min^{-1}$ $mmHg^{-1}$ ($P < 0{\cdot}01$; $t = 10$, Table 1), suggesting that the stimulus evoked vasoconstriction. The changes in central respiratory activity followed a similar pattern to those seen in the 'intact' anaesthetized animals (Table 1, Fig. 5*B*).

*Caudal f.n.* In nine anaesthetized decerebrate rabbits electrical stimulation of the caudal regions of the f.n. elicited a bradycardia of $13{\cdot}4 \pm 3{\cdot}1$ beats $min^{-1}$ and a depressor response of $19{\cdot}6 \pm 1{\cdot}63$ mmHg (Table 2, Fig. 5*A*). In five rabbits renal blood flow fell by $6{\cdot}4 \pm 1{\cdot}85$ ml $min^{-1}$ from a control of $29{\cdot}8 \pm 1{\cdot}6$ ml $min^{-1}$ ($P < 0{\cdot}01$; $t = 12$). Although renal vascular conductance was unaltered ($P > 0{\cdot}5$; $t = 12$), a transient inhibition in renal sympathetic nerve discharge was observed. This would seem to argue against any significant change in vascular resistance in this particular bed. In contrast, femoral blood flow was reduced overall by $1{\cdot}25 \pm 0{\cdot}5$ ml $min^{-1}$ from a control of $12{\cdot}5 \pm 0{\cdot}6$ ml $min^{-1}$ ($P < 0{\cdot}03$; $t = 13$). Femoral conductance was calculated to have increased by $0{\cdot}03 \pm 0{\cdot}01$ ml $min^{-1}$ $mmHg^{-1}$ ($P < 0{\cdot}02$; $t = 12$, Table 2, Fig. 5*A*), indicating a marked vasodilatation in this bed during caudal f.n. stimulation. In addition, phrenic nerve discharge was inhibited during stimulation of the caudal f.n. region. (Table 2, Fig. 5*A*).

*Pharmacological tests*

The rostral fastigial pressor response and the concomitant blood flow changes in both anaesthetized ($n = 2$) and decerebrate animals ($n = 2$) were abolished after administration of guanethidine (3·0 mg $kg^{-1}$, an adrenergic-neurone blocking drug) suggesting that the pressor effect was mediated sympathetically.

In two decerebrate rabbits atropine (1·0 mg $kg^{-1}$), a muscarinic antagonist, produced an increase in basal heart rate of 12 beats $min^{-1}$ but completely abolished the bradycardia evoked from the rostral f.n. The dose administered was sufficient to block a vagally induced bradycardia of similar magnitude to that elicited from the f.n. The bradycardia evoked by rostral f.n. stimulation in three decerebrate rabbits was severely attenuated (Fig. 6), or abolished by de-buffering the animals. Phenylephrine (20 $\mu$g), a $\beta_1$-adrenergic agonist, was injected I.V. before and after sectioning both aortic nerves and occluding both common carotid arteries to show that the animals had been de-buffered effectively (Fig. 6).

The vascular response produced by stimulation of the caudal f.n. in the decerebrate rabbit was also abolished by administration of guanethidine (3·0 mg $kg^{-1}$), in two animals. In these animals the evoked tachycardia was abolished after administration of a $\beta_1$-antagonist atenolol (0·25 mg $kg^{-1}$). This suggests that the vascular and cardiac responses are both mediated sympathetically. The dose of atenolol used produced a 9% decrease in resting heart rate and was sufficient to block the tachycardia evoked by an I.V. injection of isoprenaline (0·01 mg $kg^{-1}$), a non-specific $\beta$-agonist.

The depressor response and associated blood flow changes elicited from the caudal f.n. in the anaesthetized animal ($n = 2$) were abolished by administration of guan-

ethidine (3·0 mg $kg^{-1}$). In these animals the resting level of arterial pressure fell by 35 mmHg but was restored to control level with an infusion of noradrenaline (10·0 $\mu g\ ml^{-1}$). The bradycardia associated with the depressor response elicited from the caudal f.n. was attenuated by 60% after bilateral vagotomy or after administration of atropine (1·0 mg $kg^{-1}$). In contrast, atenolol, (0·25 mg $kg^{-1}$) attenuated the evoked bradycardia by 50% which suggests that the cardiac response to caudal f.n. stimulation is mediated both by a withdrawal of sympathetic drive and an increase in vagal activity to the heart.

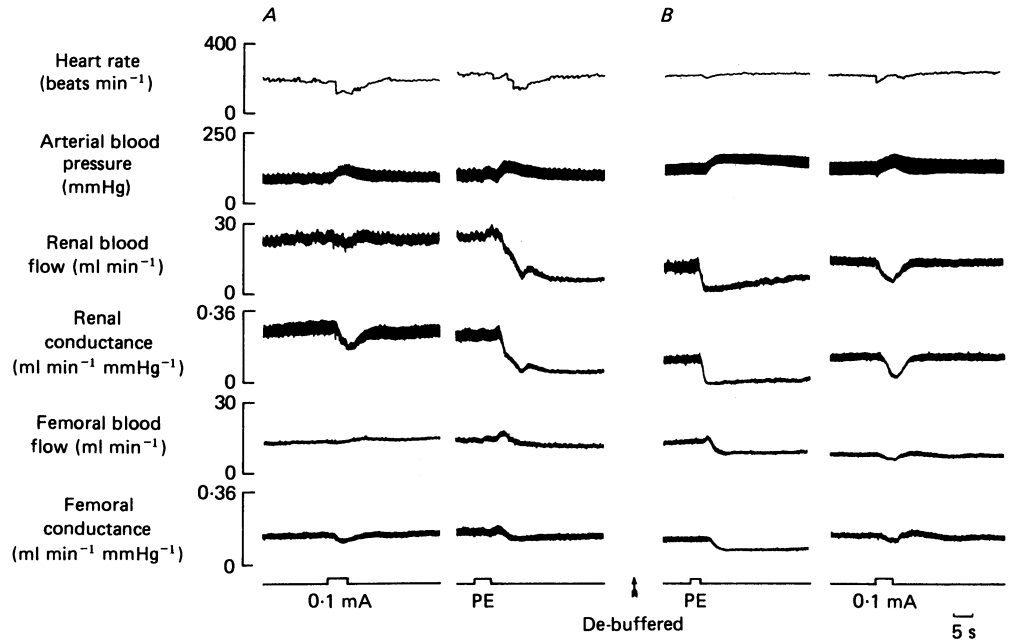


Fig. 6. Comparison of cardiovascular changes in the decerebrate rabbit during stimulation of the rostral f.n. before (*A*) and after (*B*) de-buffering. Phenylephrine (PE, 20 $\mu g$) was administered to demonstrate that the reflex bradycardia to a rise in arterial blood pressure had been blocked.

## DISCUSSION

In the present study we have shown that electrical stimulation of two distinct regions within the vicinity of the f.n. of the rabbit can elicit pronounced cardiovascular changes. Stimulation within the rostral f.n. region in either the anaesthetized or decerebrate rabbit evoked a stereotyped pattern of cardiovascular response including a vagally mediated bradycardia together with a pressor response resulting from a sympathetically induced vasoconstriction in both renal and hindlimb beds. In most cases central apnoea was also produced. In contrast, stimulation of the caudal f.n. region in the anaesthetized rabbit evoked bradycardia and a depressor effect. The cardiac response was only partially attenuated by atropine, the vascular change being in part a consequence of a withdrawal of sympathetic vasoconstrictor tone to the hindlimb. There was also an inhibition of central respiratory activity.

Stimulation of the equivalent caudal site in the decerebrate preparation elicited a sympathetically induced tachycardia, and a pressor response resulting from vasoconstriction in both renal and femoral beds, which was abolished by sympathetic blockade. Central inspiratory drive was greatly enhanced resulting in an apneusis. The administration of a small dose of anaesthetic to the decerebrate animal reversed the pattern of response evoked from the caudal f.n. region to bradycardia, a fall in arterial pressure, vasodilatation in the hindlimb and an inhibition of central inspiratory drive. This suggests that it is an effect of the anaesthetic which is responsible for the reversal in the cardiovascular pattern of response and not an effect of the decerebration. Thus, there would appear to be two distinct pathways mediating the evoked cardiovascular responses, one from the rostral region and the other from the vicinity of the caudal f.n.

The pressor response evoked by stimulation of the rostral f.n. in our experiments in the rabbit is compatible with what has been documented in a wide variety of other animal species. The heart rate response is, however, more variable. For example, the fastigial pressor response in the conscious, or anaesthetized dog is accompanied by tachycardia and an increase in force of cardiac contraction, the heart rate and blood pressure changes being secondary to increases in sympathetic activity (Dormer & Stone, 1976*a*, *b*). The arrhythmias observed by stimulating the rostral fastigial region with suprathreshold currents in this study have been reported before in the dog (Foreman, Dormer, Ohata & Stone, 1980), and cat (Al Senawi & Downman, 1983). In the cat the fastigial pressor response is associated usually with tachycardia, although in some animals a bradycardia was reported and in others no change in heart rate occurred (Miura & Reis, 1969; Achari & Downman, 1970; Achari, Al-Ubaidy & Downman, 1973). The tachycardia accompanying the fastigial pressor response in the cat was found to be mediated sympathetically (Achari & Downman, 1970; Doba & Reis, 1972). Furthermore Achari & Downman (1970) showed that stimulation of the rostral f.n. could 'inhibit' a baroreceptor-evoked bradycardia. This apparent 'inhibition' could result from a summation of the tachycardia elicited from the f.n. superimposed over the baroreceptor-mediated bradycardia, as no evidence was presented to suggest an active inhibition of the central baroreceptor reflex pathway. By comparison in the rabbit it seems that the rapid-onset bradycardia to f.n. stimulation is a genuine response, but in order to augment and maintain the bradycardia the baroreceptors would seem to be active and responding to the evoked pressor response induced by the f.n. stimulus.

In the cat the consistency of the fastigial pressor response is a consequence of a widespread vasoconstriction in the following vascular beds: small intestine, renal, cutaneous and hindlimb, as shown by plethysmography techniques (Achari & Downman, 1970) and more directly by recording blood flow changes (Doba & Reis, 1972). In a subsequent study Achari, Al-Ubaidy & Downman (1971) showed that the vasoconstriction in the small intestine and renal vascular beds was mediated by an increase in discharge of the splanchnic and renal nerves respectively. In the anaesthetized rat, electrical stimulation of the rostral f.n. evokes tachycardia and pressor effects (Chida *et al.* 1986; Henry & Connor, 1986, and D. J. Bradley, J. F. R. Paton, L. J. Preston & S. L. Snape, unpublished findings).

We are not aware of any reports describing cardiovascular responses evoked from

the caudal regions of the f.n. in any species except for a recent short report by Nisimaru & Kawaguchi (1984) in the anaesthetized rabbit. In support of our findings, they describe two separate regions within the f.n. which on stimulation evoked changes in arterial blood pressure and renal sympathetic nerve activity and from the evidence given it would seem that their sites of stimulation represent two distinct areas corresponding to the rostral and caudal divisions of the f.n. indicated in the present report. However, the response evoked from the caudal f.n. in their anaesthetized rabbits included a pressor effect and an increase in renal sympathetic nerve activity analogous to the pattern of response we see in a decerebrate animal. Under anaesthesia, stimulation of the equivalent site in our study evoked a depressor response and a transient inhibition of renal sympathetic nerve discharge. One possible explanation for this contradiction in responses between our study and Nisimaru and Kawaguchi's could be the depth of anaesthesia which has already been suggested by us as the reason for the different effects evoked from the posterior cortex (Bradley *et al.* 1987*a*).

At present, it is unclear why the observed cardiovascular responses are different between anaesthetized and unanaesthetized decerebrate animals during stimulation of the caudal f.n. (or uvula). However, administration of anaesthetic to the decerebrate rabbit will reverse the direction of the evoked response to that seen in the 'intact' anaesthetized animal, suggesting that the anaesthetic agent is responsible for the reversal and not the decerebration itself. Since the responses from the caudal f.n. are qualitatively similar to those evoked chemically from the cortex in both anaesthetized and decerebrate preparations (Bradley *et al.* 1987*b*), this rules out the possibility of efferent fibre activation in one preparation and antidromic excitation of afferent brain-stem neurones in the other. Thus the anaesthetic would appear to be exerting its effect at a brain-stem level and not within the integral pathways of the cerebellum.

In the present study we have shown that the direction of the rostral f.n. response elicited in the decerebrate animal was unaffected by administration of anaesthetic, unlike the response evoked from the caudal f.n. This suggests the presence of two distinct pathways descending from the f.n., or directly from the cerebellar cortex, to the brain stem. Furthermore, there is good anatomical evidence for two descending pathways from the caudal and rostral regions of the f.n. in the monkey (Batton, Jayaraman, Ruggiero & Carpenter, 1977), the dog (Andrezik, Dormer, Foreman & Person, 1984), and the cat (Moolenaar & Rucker, 1976, and Carpenter & Batton, 1982). Moruzzi & Pompeiano (1956), in their studies on decerebrate rigidity in the cat reported two distinct effects from rostral and caudal divisions of the f.n. which they implied were mediated by two separate pathways. Interestingly the responses they obtained from the caudal f.n. could be replicated by stimulation of the uvula. However, the problem still remains as to the origin of these two pathways and whether in this study our responses are from excitation of either fastigial cell bodies or axons of passage coursing via the f.n. as cortico-brain-stem projections.

Recently a study in the rat has shown that electrical stimulation in the rostral f.n. elicits the fastigial pressor response even after the cell bodies have been destroyed with ibotenic acid, whereas microinjections of DL-homocysteic acid and kainic acid evoked depressor responses (Chida *et al.* 1986). Moreover, Henry & Connor (1986)

failed to elicit any cardiovascular effects by microinjecting excitant or inhibitory amino acids into the rostral f.n. region of the rat, suggesting that the fastigial pressor response was a result of activation of fibres of passage. Since all cortico-nuclear fibres have an inhibitory action on cerebellar nuclear cells (Eccles, Ito & Szentagothai, 1967), and since the cardiovascular effects evoked from the caudal f.n. in this study are qualitatively identical to those evoked from the cortex, rather than being the reverse, we suggest that we are activating axons of passage during caudal f.n. stimulation. In support of this our anatomical data have shown labelled fibres in the vicinity of the caudal f.n. coursing to the brain stem following a microinjection of horseradish peroxidase into the uvula (Barrett *et al.* 1985). In addition, preliminary evidence from an ongoing study involving microinjections of excitant amino acids into the caudal and rostral regions of the f.n. have failed to elicit any cardiovascular or respiratory changes.

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