Unilateral focal lesions in the rostrolateral medulla influence chemosensitivity and breathing measured during wakefulness, sleep, and exercise

M J Morrell, P Heywood, S H Moosavi, A Guz, J Stevens

Abstract

***Objectives*—The rostrolateral medulla (RLM) has been identified in animals as an important site of chemosensitivity; in humans such site(s) have not been defined. The aim of this study was to investigate the physiological implications of unilateral lesions in the lower brainstem on the control of breathing.**

***Methods*—In 15 patients breathing was measured awake at rest, asleep, during exercise, and during CO_2 stimulation. The lesions were located clinically and by MRI; in nine patients they involved the RLM (RLM group), in six they were in the pons, cerebellum, or medial medulla (Non-RLM group). All RLM group patients, and three non-RLM group patients had ipsilateral Horner's syndrome.**

***Results*—Six of the RLM group had a ventilatory sensitivity to inhaled CO_2 ($\dot{V}/P_{ET}$ CO_2) below normal (group A: $\dot{V}/P_{ET}$ CO_2, mean, 0.87; range 0.3–1.4 $l.min^{-1}$/mm Hg). It was normal in all of the non-RLM group (group B: $\dot{V}/P_{ET}$ CO_2, mean, 3.0; range, 2.6–3.9 min^{-1}/mmHg). There was no significant difference in breathing between groups during relaxed wakefulness ($\dot{V}$, group A: 7.44 (SD 2.5) $l.min^{-1}$; group B: 6.02 (SD 1.3) $l.min^{-1}$; P_{ET} CO_2, group A: 41.0 (SD 4.2) mm g; group B: 38.3 (SD2.0) mm Hg) or during exercise ($\dot{V}/\dot{V}O_2$: group A: 21 (SD 6.0) $l.min^{-1}/l.min^{-1}$; group B: 24 (SD 7.3) $l.min^{-1}/l.min^{-1}$). During sleep, all group A had fragmented sleep compared with only one patient in group B (group A: arousals, range 13 to > 60 events/hour); moreover, in group A there was a high incidence of obstructive sleep apnoea associated with hypoxaemia.**

***Conclusion*—Patients with unilateral RLM lesions require monitoring during sleep to diagnose any sleep apnoea. The finding that unilateral RLM lesions reduce ventilatory sensitivity to inhaled CO_2 is consistent with animal studies. The reduced chemosensitivity had a minimal effect on breathing awake at rest or during exercise.**

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It has been known for some time that gross disorders of breathing can occur during both wakefulness and sleep in patients with bilateral medullary lesions (for review see Plum and Lee[1]); however, the effects of unilateral lesions are less clear. Individual case reports have led to the suggestion that respiratory control is compromised, particularly during sleep, where irregularity of breathing, hypopnoea, and obstructive apnoea may result.[2–4]

Focal lesions of the medulla oblongata can result from thrombotic occlusion in the posterior inferior cerebellar artery (PICA), the vertebral artery, or in the branches of these arteries.[5] The PICA ascends up the lateral surface of the medulla as far as the lower edge of the pons and supplies the medulla via small penetrating branches (fig 1). This anatomy means that occlusion of these vessels can produce small infarctions of the medulla. Vuilleumier *et al*[6] have shown that the topographical patterns of such lesions are likely to reflect the aetiopathogenic mechanisms which can cause them. The areas destroyed by the lesions we have described have been defined in animals as important to the control of breathing.

In recent years, the structural and functional organisation of the control of breathing within the brainstem has been extensively investigated. In animals, the work of Richter *et al*,[7] Bianchi *et al*,[8] and Smith *et al*[9] has provided an in depth description of a respiratory "oscillator" in the medulla oblongata. The influence of an animal's state of consciousness on brainstem respiratory control has been highlighted in a series of studies on breathing during wakefulness, sleep, exercise, and hypercapnia in goats[10 11] and in rats[12] with induced medullary lesions. To our knowledge, similar measurements of breathing under different conditions have not been carried out in humans with unilateral focal lesions in the medulla.

The aim of the present study was to establish in humans whether spontaneously occurring unilateral focal lesions in the medulla could result in abnormalities of breathing during relaxed wakefulness (RW), sleep, and exercise. In addition, we wanted to determine whether such lesions could be associated with a reduced ventilatory response to the inhalation of CO_2. Our studies were carried out on patients in whom the site of the lesions could be defined both clinically and with MRI. This work has been presented in preliminary form elsewhere.[13]

Methods

PATIENTS

Patients were recruited over a 2 year period from the Neurology Service at Charing Cross Hospital. All patients suspected of having a

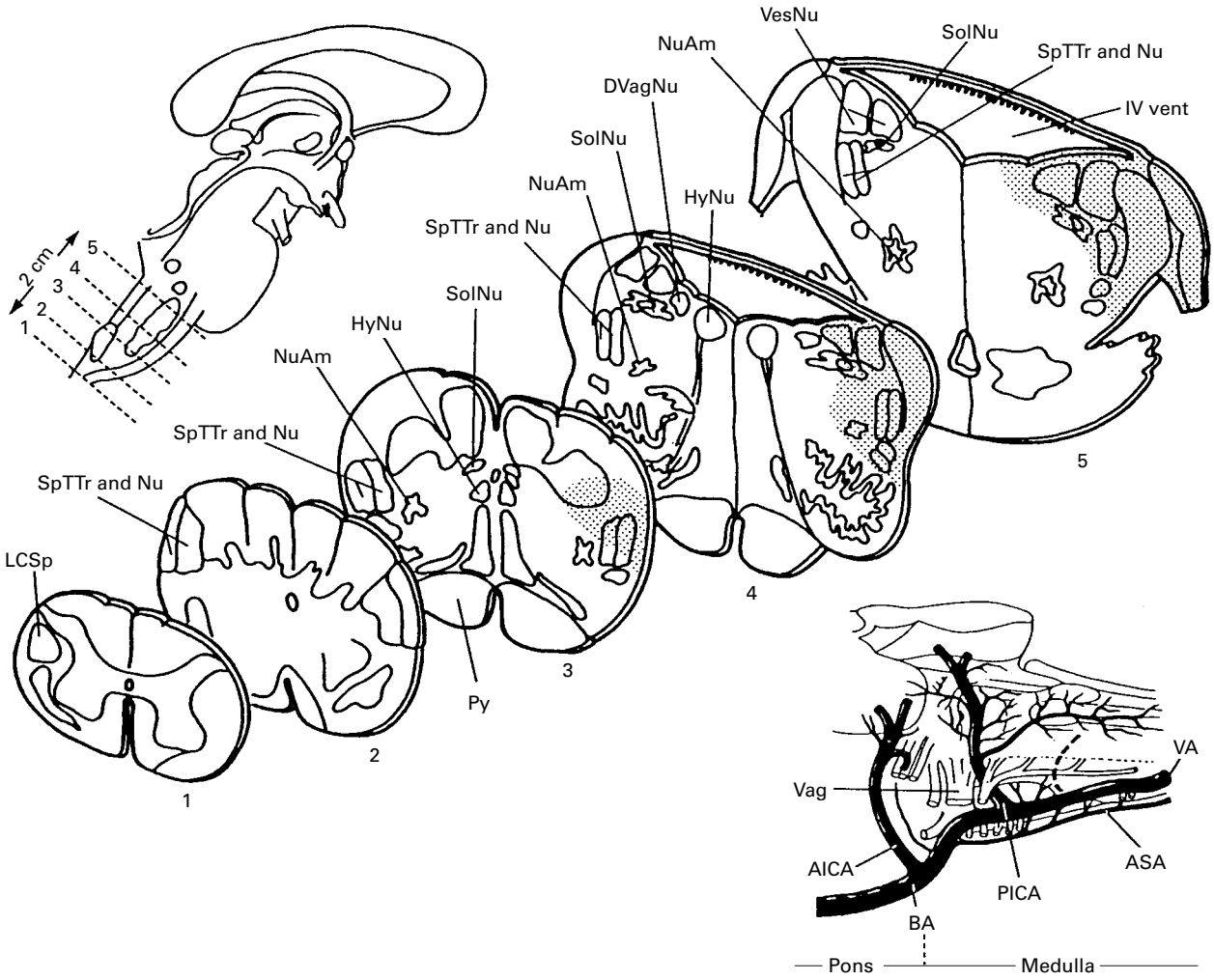

Figure 1 (A) Diagrammatic representation of the brainstem. The dotted lines mark the level at which a cross section through the medulla has been taken. (B) Each cross section numbered 1 to 5 (section 1 is the most caudal and section 5 the most rostral) are shown in detail. On each cross section the location of key structures are marked: IVth ventricle (IV vent); spinal trigeminal tract and nucleus (SPTTr and Nu); nucleus solitarius (SolNu); vestibular nuclei (VesNu); nucleus ambiguus (NuAm); hypoglossal nucleus (HyNu); dorsal vagal nucleus (DVagNu); lateral corticospinal tract (LCSp); pyramid (Py). Shaded area indicates the site of neuronal damage which occurs most often in lateral medullary syndrome. (C) The lateral surface of the medulla with the main arteries are marked: vertebral artery (VA), posterior inferior cerebellar artery (PICA), anterior spinal artery (ASA), basilar artery (BA), anterior inferior cerebellar artery (AICA), and the vagus nerve (Vag). (figure adapted with permission from Haines, 1991.[21])

focal lesion in the brainstem below the level of the midbrain were seen by one of us (PH). A detailed history was taken and full clinical examination carried out. Patients with any signs of upper airway pathology or chest disease (for example, pulmonary aspiration) were not studied; this was also true for patients with evidence of widespread neurological disease such as diffuse white matter pathology and those in whom the physical signs and symptoms were equivocal. The time between the onset of symptoms and participation in the study varied from days to a few years (table 1). All patients were studied with local ethical approval and all patients gave informed consent.

CLASSIFICATION OF NEUROLOGICAL LESIONS

Fifteen patients with unilateral brainstem lesions were studied; a description of the associated clinical signs are given in table 2. In all except one patient (3, who was unable to tolerate the procedure), MRI was also carried out to confirm the clinical localisation of each lesion. Imaging of the medulla was first optimised by applying various commercially programmed data acquisitions to two normal subjects. The instrument used (Signa, IGE Medical Systems) was operating at 1.5 Tesla in the advantage configuration at level 4.2. From the data acquisitions performed on the two control subjects, four were chosen for application to the patients. The first three were performed in all patients; the application of the last sequence depended on patient tolerance. We restricted the MRI examination times to less than 40 minutes. The data acquisition sequences used are summarised below:

(1) Sagittal spin echo, multiplanar (MEMP), TR 500/TE 10 ms, slice thickness 5 mm (interslice gap 2.5 mm), 16 images, matrix 256×192, field of view 18 cm, one excitation, study time 3.4 minutes.

(2) Axial spin echo, variable echo multiplanar (VEMP), TR 2800/TE 30 and 90 ms, slice

Table 1 Anthropometric data, lung function, ventilatory sensitivity to inhaled CO_2 and exercise data for each patient

		Anthropometric data					*Lung function data (% predicted)*		*Chemosensitivity*		
Patient No	*Time lesion to study (days)*	*Age (y)*	*Sex*	*Height (cm)*	*Weight (kg)*	*BMI (kg/m^2)*	*FEV_1/FVC*	*VC*	*$\Delta\dot{V}/\Delta CO_2$ ($l.min^{-1}$/mm Hg)*	*Correlation coefficient (r)*	*Exercise data $\Delta\dot{V}/\Delta\dot{V}O_2$ ($l.min^{-1}/l.min^{-1}$)*
RLM Group:											
1	2	42	M	185	85.0	24.8	105	88	0.7	0.95	14
2	13	64	F	163	76.5	28.8	113	69	1.4	0.96	—
3	10	59	M	164	80.0	29.7	103	46	1.2	0.98	30
4	72	69	M	165	60.5	22.2	105	91	0.5	0.89	20
5	38	47	M	174	78.0	25.8	99	96	0.3	0.84	23
6	15	38	M	172	51.2	17.3	91	85	1.1	0.90	17
7	30	52	M	168	63.6	22.5	90	111	2.2	0.98	22
8	31	51	M	171	82.0	28.0	101	95	2.2	0.98	21
9	588	44	M	169	78.5	27.5	100	64	3.2	0.98	18
Mean		52		170	72.8	25.1	101	83	1.4		21
SD		10		7	11.5	4.0	7	20	0.9		4.8
Non-RLM group:											
10	24	36	F	168	75.1	26.6	99	97	2.6	0.99	18
11	46	26	M	172	65.2	22.0	89	110	2.7	0.90	26
12	4	61	M	162	74.8	28.5	102	102	2.3	0.96	15
13	2652	58	M	160	74.1	28.9	104	89	3.1	0.98	25
14	35	59	M	167	64.0	22.9	111	91	3.9	0.97	25
15	26	68	M	170	75.1	26.0	115	90	3.1	0.98	36
mean		51		167	71.4	25.8	103	97	3.0		24
SD		16		5	5.3	2.8	9	8	0.6		7.3

Individual and mean (SD) data for rostrolateral medulla (RLM) and non-RIM groups. Anthropometric data: body mass index (BMI). Lung function data: the ratio of forced expired volume in 1 second to forced vital capacity (FEV_1/FVC), vital capacity (VC). Chemosensitivity: ventilatory sensitivity to inhaled CO_2, the slope of the response curve derived from the ventilation plotted against CO_2 ($\Delta\dot{V}/\Delta CO_2$). Exercise data: the slope of the response curve derived from the change in ventilation plotted against the change in oxygen uptake ($\Delta\dot{V}/\Delta\dot{V}O_2$). For one patient (LB) no exercise data were available (see text).

thickness 4 mm (interslice gap 2 mm), variable bandwidth, 24 images, matrix 256×192, field of view 18 cm, one excitation, study time 9.31 minutes.

(3) Gradient recalled echo sequence using spoiler gradients (SPGR), volume acquisition, axial slice thickness 1.5 mm, 64 images, matrix 256×128, field of view 20 cm, two excitations, study time 8.14 minutes.

(4) Multiplanar gradient recalled echo sequence (MPGR), flip angle 20°, axial plane, TR 240/TE 15 ms, slice thickness 5 mm (interslice gap 2.5 mm), 12 images, matrix 256×256, field of view 18 cm, four excitations, study time 8.14 minutes.

The axial plane of acquisition was oriented to be perpendicular to the floor of the fourth ventricle. Movement compensation strategies employed were: (*a*) peripheral cardiac gating, where each excitation was triggered by a finger pulse monitor, (*b*) first order gradient moment nulling, and (*c*) presaturation of superior and inferior volumes. Multiplanar reprocessing of the volumetrically acquired data set (SPGR) was performed on an independent console (Physician image processor, IGE Medical Systems) where necessary to help the clarity of the display or to increase confidence in lateralisation.

The MRI of each patient was independently reviewed by two of us (JS and PH). All lesions were visible on all acquisitions and appeared of similar size and position, though no one acquisition was the best in all patients. Localisation

Table 2 Details of the clinical signs in each patient, plus the brainstem structures involved

		Clinical signs						
		Horner's syndrome	*Ipsilateral cerebellar signs*	*Contralateral pain and temperature loss (below neck)*	*Ipsilateral pain and temperature loss (face)*	*Dysphagia*	*Contralateral upper motor*	*Ipsilateral tongue weakness*
	Area related to clinical signs							
	Level of lesion		*Ipsilateral cerebellum*	*Spinothalamic tract*	*Descending trigeminal nucleus and tract*	*Nucleus ambiguus*	*Pyramid*	*Hypoglossal nucleus*
RLM Group:								
1	5	Yes	No	No	Yes	No†	No	No
2	4–5	Yes	Yes	Yes	Yes	Yes	Yes	No
3	3–5	Yes	Yes	Yes	Yes	Yes	No	No
4	3–5	Yes	Yes	Yes	Yes	Yes	Yes	No
5	3–5	Yes	Yes	Yes	Yes	No†	No	No
6	3–4	Yes	Yes	Yes	Yes	Yes	No	No
7	4	Yes	Yes	Yes	Yes	No	No	No
8	3–4	^	Yes	Yes	Yes	No†	No	No
9	4	Yes	Yes	Yes	Yes	Yes	Yes	No
Non-RLM group:								
10	Pons	No	No	No	No	No	No	No
11	Pons	No	No	Yes	Yes	No	No	No
12	Pons	Yes	Yes	No	No	No†	No	No
13	2–4*	No	No	No	No	Yes	Yes	Yes
14	1*	Yes	Yes	Yes	Yes	No	Yes	No
15	C	Yes	Yes	No	No	No	No	No

Location of the lesion (primarily determined by the clinical findings) is given for each patient in the rostrolateral medulla (RLM) and the Non-RLM group. Numbers 1–5 refer to levels of the medulla shown in fig 1. In the Non-RLM group, 13 and 14 had lesions in the medulla, although not in the rostro lateral area (*). Signs of dysphagia had been present but resolved at the time of the study (†). Information on Horner's syndrome not given in the clinical notes; none at time of study (^). Cerebellum (C).

to the rostrolateral medullary region was determined by reference to landmarks consistently seen in all patients, though not in all acquisitions. The external landmarks (the pontomedullary junction, floor of the fourth ventricle, olives, and pyramids) were used to establish the level and lateralisation of the lesion. The internal landmarks (the pyramidal tracts and their decussation, the medial lemnisci decussation) were used to determine the presence of midline involvement. The inferior cerebellar peduncles were used to ascertain lateral involvement.

On the basis of the MRI and the clinical examination, the patients were divided into two groups: those with brainstem lesions in the area of the rostrolateral medulla (RLM group) and those with lesions which did not involve the rostrolateral medulla (non-RLM group). For each patient, the site and extent of the functional brainstem lesion is given in table 2 and the anatomical levels at which the lesions were seen are illustrated by reference to figure 1.

PHYSIOLOGICAL MEASUREMENTS

Breathing was measured in all patients during hypercapnia, relaxed wakefulness, sleep, and exercise; these tests were not necessarily carried out on the same day.

Ventilatory sensitivity to inhaled carbon dioxide

In each patient, the ventilatory sensitivity to inhaled CO_2 was measured using a rebreathing technique,[14] modified for use under normoxic conditions. Before each test, the measurement system was flushed and filled with a mixture of 6% CO_2 in air. Patients wore a nose clip and breathed via a three way tap and a mouthpiece. Rebreathing was commenced by turning the three way tap at the end of a normal expiration. Breath by breath measurements of ventilation ($\dot{V}$), respiratory frequency (fR) and tidal volume, (V_T) were determined from the respiratory airflow using an on line computerised ventilatory analysis system (Respiratory gas analyser, Buxco Electronics). Instantaneous measurements of CO_2 and O_2 gas concentrations were made at the mouth using a mass spectrometer (Centronics, MGA200). In addition, the ECG was monitored using surface electrodes and displayed on a monitor (LAN Electronics, M4-Scope). The test continued until $P_{ET}CO_2$ reached 65 mm Hg or until the patient was unable to continue due to breathlessness. Each patient was studied twice; the tests were separated by 15 minutes of rest. Linear regression of $\dot{V}$ on $P_{ET}CO_2$ over the linear portion of the response was carried out for each of the two tests; slopes with *r* values below 0.80 were not accepted for analysis. The mean of the two slopes was taken as representative of the hypercapnic ventilatory sensitivity; there was little variance between the two tests (mean difference (SD): RLM group, 0.17 (0.62) $l.min^{-1}$ /mm Hg; non-RLM group 0.31 (0.56) $l.min^{-1}$ /mm Hg). In two patients (6 and 9) only one slope had an acceptable *r* value. The normal range of the ventilatory sensitivity to inhaled CO_2 in our laboratory with this technique is mean (SD) 3.5 (1.2); range 1.7–6.2 $l.min^{-1}$ /mmHg.[15]

RELAXED WAKEFULNESS AND SLEEP

Five minutes of breathing during RW was measured before the sleep study. During the RW measurements, the patient lay on the bed wearing a blindfold and headphones, to reduce sensory input[16]; patients were monitored by means of a video. RW was confirmed from monitoring the record of two EEGs (EEG; C3-A2 and C4-A1), two electro-occulograms (EOG; F7-A2 and F8-A2) and one EMG (chin EMG) made using a Mingograf EEG 10 recorder (Siemens-Elema). Breathing was measured from recordings of chest wall and abdominal movements made using a DC coupled, respiratory inductance plethysmograph (RIP; Respitrace Co ambulatory monitoring). The RIP was calibrated with the patient simultaneously breathing into a rolling seal spirometer (Spiroflow, PK Morgan). Expired airflow was used to derive the $P_{ET}CO_2$ using an infrared gas analyser (LB2, Beckman Instruments). Ear arterial oxygen saturation (SaO_2) was estimated using a pulse oximeter (Biox 3700, Ohmeda). V_T, total breath duration (T_{TOT}), $\dot{V}$, and P_{ETCO_2} were calculated on a breath by breath basis.

Measurements of breathing during sleep were made between 2100 and 0700 hours. Sleep stages were scored from 30 second epochs according to the standard criteria.[17] The first period of uninterrupted stage IV Non-REM sleep longer than 5 minutes was chosen for analysis of the sleep related respiratory variables, provided no signs of hypoventilation or apnoea secondary to mechanical obstruction were seen. Apnoeas were classified as obstructive when paradoxical ribcage and abdominal movements occurred during an absence of a P_{ETCO_2} signal (index of airflow) for>10 seconds duration, together with a resumption of breathing associated with a loud snoring or snorting sound and on most occasions an arousal. Apnoeas were classified as central when the cessation of airflow was not associated with respiratory effort. Mixed apnoeas were central apnoeas that progressed into obstruction. Hypopnoea was defined as the presence of a reduced amplitude of ribcage and abdominal movements in association with loud snoring sounds during inspiration and/or expiration. Where possible, signs were confirmed using oesophageal pressure (Poes) and airflow signals (see below).

Three patients (3, 4, and 13) were studied on two occasions during sleep; in each case, the second study was carried out to confirm the diagnosis and to evaluate treatment. During the second study, measurements of Poes were made as an index of respiratory effort. A balloon tipped catheter was passed through the nose and positioned in the mid-third of the oesophagus (about 40 cm from the nares); it was connected to a differential pressure amplifier (MP-45, (SD 80) cm H_2O, Validyne). In these patients, all data presented are from the first study (without an oesophageal catheter). In one patient (6, who could only be studied on one occasion) oesophageal pressure (Poes) monitoring was carried out during the initial sleep study.

Exercise

All patients performed a progressive exercise protocol in a laboratory maintained at an ambient temperature between 18°C and 23°C. Patients wore a nose clip and breathed through a mouthpiece attached to a thermostatically heated Fleisch No 2 pneumotachograph. Exercise was performed with the patient seated in a comfortable chair with their feet strapped to the pedals of a cycle ergometer. Three patients with unilateral leg weakness (4, 9, and 13) performed exercise with one leg only using specially designed exercise equipment[18]; the weak leg was kept relaxed in a comfortable position. After one minute of resting cardiorespiratory measurements, 4 minutes of rolling basal measurements were made, during which the patient pedalled against a negligible resistance. The patients were encouraged to maintain a pedal rate of between 50 and 60 revolutions per minute. One minute incremental workloads were set taking account of the patient's clinical weakness; individual increments varied between 5 and 25 W/minute. An automated exercise analysis system (Ergostar, Fenyves, and Gut) provided 30 second average measurements of heart rate, fR, V_T, $\dot{V}$, and P_{ETCO_2} corrected to provide a better estimate of P_{ETCO_2}.[19] ECG and SaO_2 were monitored continuously throughout exercise. In addition, blood pressure was measured every 2 minutes. The test was terminated when (*a*) the patients were unable to continue, (*b*) the predicted maximum heart rate was achieved, (*c*) an excessive rise in systolic blood pressure occurred, or (*d*) when an ECG abnormality was detected.

Thirty second averaged data from each progressive exercise test were subjected to linear regression by a least squares fit of $\dot{V}$ on oxygen uptake ($\dot{V}O_2$). The slope of this regression provided a quantitative index of individual ventilatory sensitivity to progressive exercise. In the cases where the threshold for anaerobiosis (lactate threshold[20]) was exceeded (as shown by the upward inflection of the ventilatory equivalent for $\dot{V}O_2$), only the 30 second average measurements between the end of the rolling basal period and this upward inflection were included in the linear regression.

STATISTICAL ANALYSIS

Comparisons of group mean variables (RLM group *v* non-RLM group) for anthropometric, lung function, ventilatory sensitivity to inhaled CO_2, and exercise data were made using a two tailed unpaired *t* test. Comparison of group mean variables (group A *v* group B) for breathing pattern (T_{TOT}, V_T, $\dot{V}$, and P_{ETCO_2}) measured during RW, were made using a one way analysis of variance (ANOVA). For all tests the level of significance was taken as $p<0.05$.

Results

CLINICAL PRESENTATION

For each patient, the anthropometric data and details of lung function, ventilatory sensitivity to inhaled CO_2 and exercise are given in table 1. There was no significant difference between the two groups for age (p=0.95), height (p=0.27), weight (p=0.78) and the degree of obesity as judged by the body mass index (BMI: height / weight^2; p = 0.71). Two patients (2 and 9) had a reduced lung vital capacity (VC), and one patient (3) had lung restriction due to diffuse interstitial lung disease of unknown cause. However, there was no significant difference between the two groups in the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC, p=0.55) or in VC (p=0.13). In each patient, the location of the lesion was defined clinically (table 2) and confirmed by MRI. An example of MRI in a patient (6) with an RLM lesion is shown in figure 2.

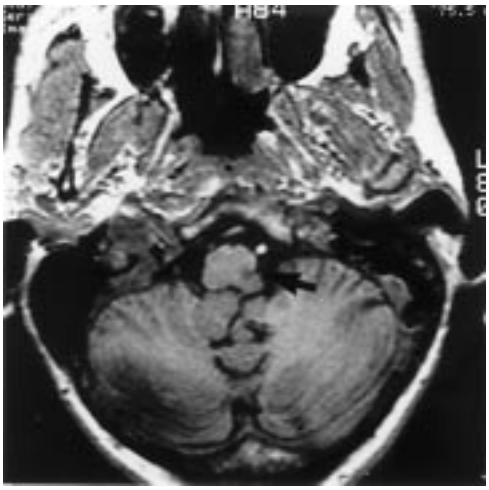

Figure 2 An axial MRI through the upper brainstem and cerebellum (SPGR, data acquisition method No 3-see methods) from patient 6. A small, low density lesion is shown just deep to the left lateral surface of the rostral part of the medulla oblongata, between the olive and inferior cerebellar peduncle (arrow); it was visible on three contiguous images, giving it a longitudinal extent of about 4.5 mm. The high signal in the left vertebral artery adjacent to the olive is produced by flowing blood and is a normal signal for this type of data acquisition.

VENTILATORY SENSITIVITY TO INHALED CARBON DIOXIDE

The individual ventilatory sensitivities to inhaled CO_2 are shown diagrammatically in figure 3. For each patient the slope of the ventilatory response to inhaled CO_2 and the corre-

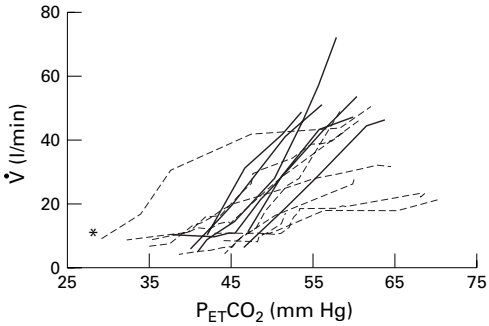

Figure 3 A diagrammatic representation of the awake ventilatory sensitivity to inhaled CO_2 ($\dot{V}$=ventilation; P_{ETCO_2} = end tidal carbon dioxide) in patients with lesions involving the rostrolateral medulla (RLM=dotted lines) and patients with lesions not involving the rostrolateral medulla (non-RLM=full lines). In one patient (5) an abnormally high level of ventilation occurred; note that this chronic hyperventilation was not exacerbated during hypercapnia.*

Table 3 Breathing during relaxed wakefulness

	T_{TOT} (s)	V_T (l)	$\dot{V}$ (l/min)	P_{ETCO_2} (mm Hg)
Group A	5.4 (2.1)	0.58 (0.2)	7.44 (2.5)	41.0 (4.2)
Group B	4.2 (0.4)	0.43 (0.1)	6.02 (1.31)	38.3 (2.0)

Group mean values (SD) for breath duration (T_{TOT}), tidal volume (V_T), ventilation, ($\dot{V}$) and end tidal PCO_2 (P_{ETCO_2}) measured during relaxed wakefulness in patients with an RLM lesion plus a low ventilatory sensitivity to inhaled CO_2 (group A; n=6) and patients of the non-RLM group with a normal sensitivity to inhaled CO_2 (Group B; n=5).

Table 4 Summary of sleep patterns

Patient	Total sleep time (% of study duration)	Time to sleep onset (min)	Sleep stages (% of total sleep time)			Arousals (events/hour)
			I/II	III/IV	REM	
Group A						
1	56	23	92	0	8	13
2	—	*12	—	—	—	—
3	71	15	100	0	0	>60
4	79	14	88	0	12	>60
5	82	24	55	22	23	14
6	69	32	43	32	24	21
Group B						
10	41	17	43	57	0	0
11	82	15	31	23	47	0
12	40	92	51	37	11	0
13	60	20	78	10	12	>60
14	67	44	48	30	22	0
15	39	36	31	42	27	0

Group A and B=patients with a reduced and normal ventilatory sensitivity to inhaled CO_2 respectively. For patient 2, time to sleep onset (*) was taken from the first indication of slowing of the EEG frequency; other sleep parameters were not calculated because the EEG was atypical (see text).

lation coefficient (*r*) are given in table 1. Six of the nine RLM group patients had a reduced CO_2 sensitivity. The remaining three patients (7, 8, and 9) were found to have a normal hypercapnic ventilatory response despite having a lesion in the RLM. In each of these patients, the lesion was relatively caudal and did not extend up into level 5 (fig 1). For the non-RLM group all responses were within normal limits. There was a significant difference between the group mean slope of the ventilatory response to inhaled CO_2 in the RLM group compared with the non-RLM group (p=0.004). Overall, we found that patients with unilateral damage to the RLM had a reduced ventilatory sensitivity to inhaled CO_2.

BREATHING DURING RELAXED WAKEFULNESS AND SLEEP

Group mean (SD) of all the respiratory variables (T_{TOT}, V_T, $\dot{V}$, and P_{ETCO_2}), measured during RW, in the RLM group patients with a reduced sensitivity to inhaled CO_2 (group A) and in five of the non-RLM group patients with normal sensitivity to inhaled CO_2 (group B) are shown in table 3. There was no significant difference between group A and group B for any of the respiratory variables measured. Both group A and group B had a similar mean P_{ETCO_2}, with the exception of one subject (3) (RW: P_{ETCO_2}, 48 mm Hg) in whom the diffuse lung shadowing had been noted. One non-RLM patient (13) was not included in this analysis because we were unable to quantify the CO_2 measurements for technical reasons.

All patients were able to sleep; the total sleep time and distribution of sleep stages varied greatly. Details of the sleep patterns are shown in table 4. In one group A patient (2), sleep stages were not scored because the EEG wave forms were atypical and did not conform to the standard criteria.[17] All group A patients and one group B patient (13), were found to have frequent short arousals from sleep (13 to>60 arousals/hour of sleep). In group B, three patients (10, 12, and 15) had a total sleep time below 50% of the study time; they reported difficulty sleeping in the laboratory.

The incidence of sleep disordered breathing, either central in origin, or secondary to mechanical obstruction, was higher in group A than in group B. In group A, four patients (1, 2, 3, 5) had obstructive sleep apnoea/hypopnoeas, compared with only one patient in group B (13); this patient had a unilateral tongue weakness with a medial medullary syndrome (table 2). The BMI was similar in both groups (table 1). In group A, two patients (1 and 2), had very fragmented sleep despite the low apnoea/hypopnoea index. Unequivocal central hypoventilation (in the absence of mechanical obstruction) was not seen in any of the

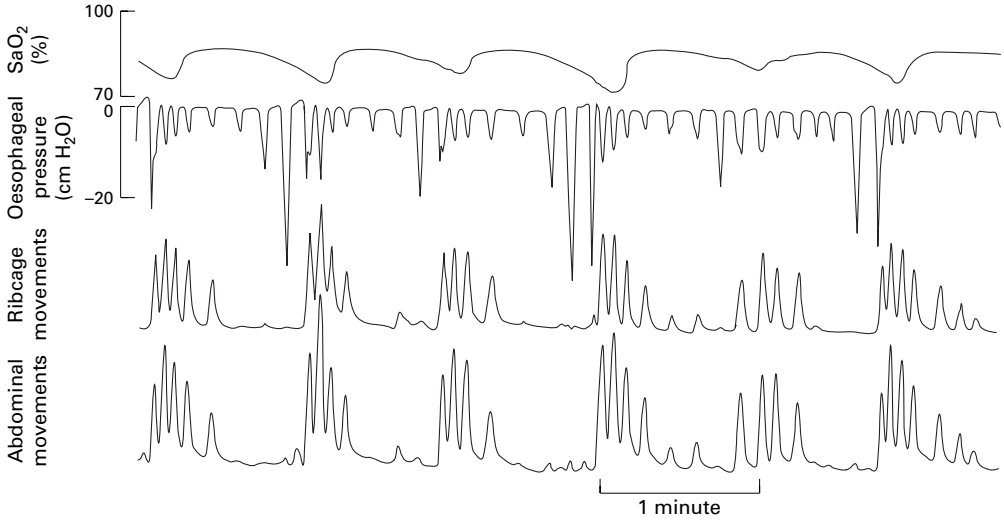

Figure 4 Original recording in one patient (4) during non-REM sleep. Oxygen saturation (SaO_2) shows transient dips associated with negative intrathoracic pressure and reduced respiratory movements, indicating upper airway obstruction and sleep apnoea.

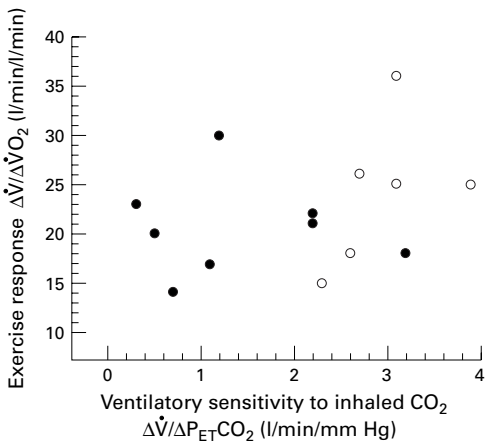

Figure 5 Individual ventilatory responses to exercise (defined as the slope of the linear regression of ventilation on oxygen uptake, $\Delta\dot{V}/\Delta\dot{V}O_2$, between the rolling basal period and the onset of anaerobiosis) plotted in relation to that person's ventilatory sensitivity to inhaled CO_2 (defined as the slope of the linear regression of ventilation on P_{ETCO_2}, $\Delta\dot{V}/\Delta P_{ETCO_2}$) for each patient (RLM group closed circles; non-RLM group open circles).

patients. However, in group A, one patient (4) was found to have frequent mixed apnoeas (>60 apnoeas/hour sleep) (fig 4); this patient had a normal BMI and a low sensitivity to inhaled CO_2 (table 1).

Comparisons of breathing during wakefulness and sleep for group A and B patients were hampered by the fact that in group A only two patients (5 and 6) achieved stable stage IV sleep during which regular breathing with no signs of mechanical obstruction of the upper airway were seen. In these two patients, in whom the sensitivity to inhaled CO_2 was reduced (table 1), the reduction in breathing asleep compared with that which occurred during RW was substantial (P_{ETCO_2} , RW *v* NREM sleep; patient 5: 35.7 mm Hg *v* 39.1 mm Hg; patient 6: 40.8 mm Hg *v* 42.8 mm Hg). In group B, regular breathing during stage IV sleep occurred in four subjects (group mean (range): RW *v* NREM sleep, 37.6 (35.9—40) mm Hg *v* 38.3 (36.3—40.4) mm Hg).

BREATHING DURING EXERCISE

For all but one group A patient (2), the ventilatory sensitivity to exercise ($\Delta\dot{V}/\Delta\dot{V}O_2$) is given in table 1; patient 2 was unable to exercise beyond the rolling basal exercise period. $\dot{V}O_2$ increased in group A up to a mean of 1.39 $l.min^{-1}$ (range 1.06–1.97 $l.min^{-1}$), and in group B up to a mean of 1.57 $l.min^{-1}$ (range 0.99–2.19 $l.min^{-1}$). $\dot{V}$ increased in group A up to a range of 21–26 $l.min^{-1}$, and in group B up to a range of 15–41 $l.min^{-1}$; fR changed little. The baseline $P_{ET}CO_2$ ranged from 28–45 mm Hg; it remained almost constant throughout most of the test and only began to decrease at a $\dot{V}O_2$ of about 1.2 $l.min^{-1}$; this hyperventilation was taken as evidence that anaerobic metabolism was developing at this time.[20] The absence of any relation between the ventilatory response to exercise and the response to inhaled CO_2 in the RLM and the non-RLM groups is shown in fig 5.

Discussion

This study shows that patients with a unilateral lesion in the rostrolateral medulla have a poor ventilatory response to inhaled CO_2. Breathing is seriously disrupted during sleep with a high incidence of obstructive apnoea. When awake, patients breath normally both at rest and during exercise.

MEASUREMENT OF CHEMOSENSITIVITY

In the present study, we measured the ventilatory response to inhaled CO_2 when awake, using a well established, non-invasive clinical method[14] as an overall test of ventilatory chemosensitivity under normoxic conditions. This test produces a measurement of the ventilatory sensitivity to CO_2 above the level of P_ACO_2 before the rebreathing. We cannot know how the sensitivities measured in our study relate to the sensitivity around the P_ACO_2 level at rest; this may be an important consideration in the interpretation of our results under the different states studied.

LOCATION OF THE LESIONS

We have studied patients with vascular occlusions in the PICA or its branches,[5 6 21] which produced focal unilateral lesions; the associated clinical signs suggested the anatomical location in the rostrocaudal direction, and verification of this site was possible using MRI. The uniformity of the finding of Horner's syndrome in the RLM group, in whom the ventilatory sensitivity to inhaled CO_2 was reduced, provides additional support for the anatomical site of the lesion. Animals with chemically induced unilateral lesions in the retrotrapezoid and subretrofacial nuclear areas have an absent or reduced increased phrenic nerve output during inhalation of CO_2; in addition the respiratory related amplitude of the integrated activity in the cervical sympathetic nerve is also reduced.[22] The neurons in these areas give rise to sympathetic outflow[23]; in the cat, electrical stimulation in these regions can cause ipsilateral pupillary dilatation.[24] Taken together these findings suggest that both in animals and in humans, the neuronal groups concerned with sympathetic output and respiratory control are intermingled at these sites.

Obtaining clear images of the medulla is difficult. The structure is both small and subject to complex cardiosynchronous oscillatory movement in the CSF and vertebral arteries; the second also often distorts the anterolateral contour by compression. This motion introduces artefacts which project into the images of the medulla and this reduces the sensitivity of detecting changes in tissue structure. Although these disturbing effects can be minimised by the use of a range of strategies, performance will still vary even with images of similar specification. In the present study, the use of varied MRI sequences gave us confidence in defining the extent and localisation of the clinical lesions. We preferred to use internal and external landmarks rather than grids and templates used by others.[25]

SLEEP, WAKEFULNESS, AND EXERCISE

In the present study unilateral lesions in the RLM resulted in sleep disordered breathing and in arousals from sleep which were independent of any respiratory related disturbance in sleep patterns. The fact that some of the patients were unable to maintain sleep suggests that neuronal damage was present in regions of the brainstem concerned with the sleep/wake cycle. In group A the high incidence of sleep and breathing disturbances meant that we found it difficult to interpret the importance of the reduced sensitivity to inhaled CO_2 on breathing during sleep, because long periods of steady breathing during deep sleep did not occur. Nevertheless, in two patients who had some stability of breathing during sleep, a reduction in ventilation did occur.

The frequency of upper airway obstruction, particularly in the absence of any neurological lesions of the hypoglossal nerve(s), is difficult to interpret. It may have resulted from the unilateral lack of coordination of the upper airway muscles, due to the lesion affecting the deeper structure of the nucleus ambiguus. In the RLM group it is noteworthy that three of the five patients with dysphagia (at the time of study) also had sleep disordered breathing with obstruction of the upper airway. Our findings are consistent with the case report of a patient with a unilateral lesion in the medulla and obstructive sleep apnoea by Chaudhary *et al*.[2] It is also of interest that acute lesions produced by cooling in the rostral ventrolateral medulla of the awake goat can result in obstruction of the upper airway, necessitating a tracheostomy so that the breathing in these animals could be studied (fig 5 in Forster *et al*[26]). These workers suggested that their findings could be explained, if cooling decreased the inspiratory related facilitation of the upper airway muscles to a greater degree than the diaphragm.

The maintenance of normal ventilation during wakefulness, when the ventilatory sensitivity to inhaled CO_2 was minimal, emphasises the importance of the wakefulness drive(s) on breathing.[27] A similar dissociation between the normality of the ventilatory response to exercise and the reduced or absent ventilatory chemosensitivity occurs in children with the congenital hypoventilation syndrome.[28] The lack of correlation between the ventilatory response to CO_2 and the response due to exercise, in these patients and in the present study, illustrates that the mechanisms responsible for these responses are likely to be different.

COMPARABILITY OF ANATOMICAL SITES: EXPERIMENTAL LESIONS IN ANIMALS AND CLINICAL LESIONS IN HUMANS

There are clear similarities between our physiological findings in these patients and the evidence from animal studies—that is, the effect of unilateral lesions in the rostral medulla causing a reduction of ventilatory sensitivity to CO_2 with maintenance of normal ventilation awake but not asleep.[12 29 30] Our human studies add the evidence of a normal ventilatory response to exercise. However, the animal studies have focused on rostral ventrolateral medullary lesions. In our studies, the lesions are rostral but lateral or even dorsolateral, as shown on the MRI in figure 2. The rostral dorsolateral medulla is full of neuronal pools and tracts (fig 1), which when damaged give rise to clear cut physical "signs", this is not so for the ventrolateral medulla, lateral to the pyramids. We cannot therefore be confident that the anatomical sites of the relevant lesions in humans are comparable with the sites of the lesions induced in rats, cats, and goats because the shape of the brainstem and the anatomical organisation within are different. Comparisons between the brainstem of humans and that of animals is made more difficult by the huge development of the ventral pons in humans, consequent on the presence of the major corticopontocerebellar tracts. In the laboratory animals, this development would necessitate the "migration" of ventral structures to a more lateral or dorsolateral position.

RECOVERY OF FUNCTION

Partial or even complete recovery is not rare in patients with lateral medullary syndrome. Some recovery of function did occur in our patients; this was particularly shown by the recovery from dysphagia (table 2). In our study there was a large variation in time between the onset of the lesion and when we did our investigations (table 1). This would have resulted in an opportunity for recovery in some patients but not in others. It is of note that patients 9 and 13 (with the longest time to study) had a ventilatory sensitivity to inhaled CO_2 which was within our normal range. We cannot be certain, particularly in these patients, that the ventilatory sensitivity measured soon after the lesion developed would not have been normal.

SUMMARY OF FINDINGS AND CLINICAL IMPLICATIONS

The findings of this clinical study strongly support the experimental evidence from animal investigations that the RLM is a key area for the full expression of the ventilatory response to inhaled CO_2. In addition, the results show that breathing is normal during wakefulness, both at rest and on exercise in patients with a unilateral lesion in this area of the brainstem. During sleep, both breathing and sleep patterns are seriously disrupted. These findings during sleep have clinical implications, particularly in the cases where the sleep disordered breathing was accompanied by repeated hypoxaemic episodes. In patients with ischaemic insult, it would seem important to obviate an additional arterial hypoxaemic insult to the brainstem. Any sleep related hypoxia can be relatively easily measured using some form of nocturnal monitoring.

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1 Plum F, Leigh RJ. Abnormalities of central mechanisms. In: Hornbein TF, ed. *Regulation of breathing*. New York: Marcel Dekker, *Lung Biology in Health and Disease 1981;***12***:989–1067*.
2 Chaudhary BA, Elguindi AS, King DW. Obstructive sleep apnea after lateral medullary syndrome. *South Med J* 1982; **75**:65–7.
3 Bogousslavsky J, Khurana R, Deruaz JP, *et al*. Respiratory failure and unilateral caudal brainstem infarction. *Ann Neurol* 1990;**28**:668–73.
4 Vigerhoets F, Bogousslavsky J. Respiratory dysfunction in neuromuscular disease, respiratory dysfunction in stroke. *Clin Chest Med* 1994;**15**:729–37.
5 Martin PJ. Vertebrobasilar ischaemia. *Q J Med* 1998;**91**: 799–811.
6 Vuilleumier P, Bogousslavsky J, Regli F. Infarction of the lower brainstem: clinical, aetiological and MRI-topographical correlations. *Brain* 1995;**118**:1013–25.
7 Richter D, Ballantyne D, Remmers J. How is the respiratory rhythm generated*? News in the Physiological Sciences* 1986;109–12.
8 Bianchi AL, Grelot L, Iscoe S, *et al*. Electrophysiological properties of the rostral medullary areas in the cat. *J Physiol Paris* 1988;**104**:293–310.
9 Smith JC, Elllenberger HH, Ballanyi K, *et al*. Pre-Botzinger complex: a brainstem region that may generate respiratory rhythm in mammals. *Science* 1991;**254**:726–9.
10 Forster HV, Ohtake PJ, Lowry TF. Effects of breathing on surface ventrolateral medullary cooling in awake, anaesthetised and asleep goats. *Respir Physiol* 1997;**110**:187–97.
11 Forster HV, Pan LG, Lowry TF, *et al*. Breathing of awake goats during prolonged dysfunction of caudal M ventrolateral medullary neurones. *J Appl Physiol* 1998;**84**:129–40.
12 Akilesh MP, Kemper M, Li A, *et al*. Effects of unilateral lesions of retrotrapezoid nucleus on breathing in awake rats. *J Appl Physiol* 1997;**82**:469–79.
13 Heywood P, Morrell MJ, Moosavi S, *et al*. Ventilatory control awake, asleep and during exercise in man with unilateral rostral ventrolateral medullary lesions. *International Congress of Physiological Societies*. Glasgow: The Physiological Society of London, 1993:282.
14 Read D. A clinical method for assessing the ventilatory response to carbon dioxide. *Australasian Annals of Medicine* 1967;**16**:20–30.
15 Adams L, Chronos N, Lane R, *et al*. The measurement of breathlessness induced in normal subjects: validity of two scaling techniques. *Clin Sci* 1985;**69**:7–16.
16 Shea SA, Walter J, Murphy K, *et al*. Evidence for individuality of breathing patterns in resting healthy man. *Respir Physiol* 1987;**68**:331–44.
17 Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects*. Bethesda, Maryland: US Government Printing Office, 1968.
18 Innes AJ, DeCourt SC, Eans PJ, *et al*. Central command influences cardiopulmonary response to dynamic exercise in humans with unilateral weakness. *J Physiol Lond* 1992;**448**:551–63.
19 Jones NL, Robertson DG, Kan JW. Differences between end-tidal and afferent PCO_2 in exercise. *J Appl Physiol* 1979;**47**:954–60.
20 Wasserman K, Hansen JE, Sue DY, *et al*. Principles of exercise testing and interpretation. Philadelphia: Lea and Febiger, 1987.
21 Haines DE. *Neuroanatomy: an atlas of structures, sections and systems*. 3rd ed. Baltimore: Williams and Wilkins, 1991.
22 Nattie EE, Blanchford C, Aihua L. Retrofacial lesions: effects on CO_2 sensitive phrenic and sympathetic nerve activity. *J Appl Physiol* 1992;**73**:137–25.
23 Dampney R. The subretrofacial nucleus: it's pivotal role in cardiovascular regulation. *News in Physiological Sciences* 1990;**5**:63–7.
24 McAllen RM. Action and specificity of ventral medullary vesopressor neurones in the cat. *Neuroscience* 1996;**18**:51–9.
25 Bronstein A, Morris J, duBoulay G, *et al*. Abnormalities of horizontal gaze. Clinical, oculorgraphic and MRI findings. *J Neurol Neurosurg Psychiatry* 1990;**53**:194–9.
26 Forster HV, Lowery TF, Ohtake PJ, *et al*. Differential effect of ventrolateral medullary cooling on respiratory muscle of goats. *J Appl Physiol* 1995;**78**:1859–67.
27 Fink B. Influence of cerebral activity in wakefulness on regulation of breathing. *J Appl Physiol* 1961;**16**:15–20.
28 Shea SA, Andres LP, Shannon DC, *et al*. Ventilatory responses to exercise in humans lacking ventilatory chemosensitivity. *J Physiol Lond* 1993;**468**:623–40.
29 Nattie EE, Li A. Retrotrapezoid nucleus lesions decrease phrenic activity and CO_2 sensitivity in rats. *Respir Physiol* 1994;**97**:63–77.
30 Nattie EE, Li A. Rat retrotrapezoid nucleus iono- and metabotrophic glutamate receptors and the control of breathing. *J Appl Physiol* 1995;**78**:153–63.