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Effects of Medullary Midline Lesions on Cough and Other Airway Reflexes in Anaesthetized Cats

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Summary

The involvement of rapheal and medial parts of the medullary reticular formation in both generation of airway reflexes and changes in breathing were studied in 18 chloralose or pentobarbitone anaesthetized, non-paralyzed cats. Chemical lesions to the medullary midline region (0–4 mm rostral to the obex) produced by localized injections of the neurotoxin kainic acid regularly abolished the cough reflexes evoked from the tracheobronchial and laryngopharyngeal regions and in most cases also the expiration reflex induced from the glottal area. The aspiration reflex elicited from the nasopharynx was spared, but was less intense. However, the signs of cough and expiration reflexes were preserved in the neurogram of the recurrent laryngeal nerve. The experiments have shown the importance of raphe nuclei and other medullary midline structures for the occurrence of cough and expiration reflexes. One possible explanation for the elimination of these expulsive processes is the removal of an important source of facilitatory input to the spinal respiratory motoneurons or to the brainstem circuitries that mediate cough and expiration reflexes . The role of the medullary midline in modulation of eupnoeic breathing and blood pressure is also discussed.

Key words

Medullary midline – Raphe nuclei – Cough – Aspiration and Expiration reflexes – Kainic acid lesion

Introduction

The brainstem circuitries that produce poly- or oligosynaptic airway reflexes such as the cough, expiration (ER) and aspiration (AR) reflexes are considered to consist of input pathways, a central coordinating network, and pre-motor and motor outputs. Cough is the most important defensive airways reflex that can be easily evoked in the cat by mechanical stimuli to the rapidly adapting vagal receptors of the tracheobronchial (TB-cough) or laryngopharyngeal (LPh-cough) mucosa (Korpáš and Tomori 1979, Widdicombe 1995). Previous studies suggested the existence of an independent "cough centre" situated hypothetically either in the medial part of the dorsal medulla (Borison 1948, Chakravarty *et al.* 1956, Chou and Wang 1975) or in the region of the nucl. ambiguus (Bucher 1958) and nucl. reticularis parvocellularis (Kasé 1980). In addition, the modulatory effect of the rostral part of the pons on the pattern of cough and ER was also described (Dubi 1959, Jakuš *et al.* 1987a). Mapping of brainstem neurons using the C-Fos like immunoreactive method in "fictive" laryngeal cough, has recently revealed the involvement of respiratory neurons localized in the dorsal and ventral medullary respiratory groups, as well as those in medial and lateral reticular, raphe and pontine parabrachial nuclei (Gestreau *et al.* 1994, 1997).

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Considerably less is known about the central mechanisms integrating the AR from the nasopharyngeal region and ER from the vocal folds. Hypothetically, it was assumed that the higher-order neurons of the AR might be located in the ventrolateral part of nucl. tractus solitarii (Batsel and Lines 1973) in the cat, or more probably in the lateral tegmental field of the medulla (Fung *et al.* 1994). The pattern of discharge of a great number of medullary respiratory neurons responsible for normal respiratory rhythmogenesis is markedly altered during coughing (Engelhorn and Weller 1965, Jakuš *et al.* 1985, Oku *et al.* 1994, Gestreau *et al.* 1996, Shannon *et al.* 1996), as well as during AR (Batsel and Lines 1973, Jakuš *et al.* 1985, 1987b, Fung *et al.* 1995) and ER (Hanáček *et al.* 1977, Jakuš *et al.* 1985, Bongianni *et al.* 1988, Dyachenko 1990, Lawson *et al.* 1991). It thus seems that the central pattern generator of breathing additionally produces the motor program for these reflexes. However, the proper location of the second- and higher-order neurons in processing the aforementioned reflexes remains unknown. The modulatory role of the serotoninergic medullary raphe structures in the generation of respiratory rhythmicity has recently been shown (Holtman *et al.* 1986, Millhorn 1986, Lindsey *et al.* 1992, Budziňska and Romaniuk 1995, Lalley *et al.* 1997). Similarly, their influence on sympathetic cardiovascular outflow (Morrison and Gebber 1984, Gilbey *et al.* 1995) and on the postural tone of skeletal muscles (Mori 1989, Budziňska and Romaniuk 1995) as well as on the elicitation of vomiting (Miller *et al.* 1996) have already been reported. The present study was designed to examine the effects of kainic acid lesions in the midline medullary structures in evoking and modifying the character and intensity of TB- and LPh-coughs, the AR and ER, evoked by mechanical stimulation of individual airway areas. The effects of lesions on eupnoeic breathing and systemic blood pressure are also described.

Methods

The experiments were carried out on 18 non-paralyzed adult cats of either sex (mean body weight 2.81±0.17 kg) divided into two experimental groups. The first group included 10 cats, anaesthetized with 3 % halothan inhalation followed by α-chloralose (Merck, 55 mg/kg) i.v. The second group consisted of 8 cats under general sodium pentobarbitone anaesthesia (Pentobarbital, Spofa) induced by an initial dose of 40 mg/kg i.v. and maintenance doses 5 mg/kg/h. Supplemental doses of pentobarbitone were given if the blood pressure or respiratory frequency increased spontaneously or in response to surgical procedures or pinching a paw. Airway reflexes were usually evoked at least 20 min after the administration of an additional dose of pentobarbitone.

The general surgical preparation was the same in both experimental groups. After tracheostomy the right femoral vein and artery were cannulated for further venous injections and measurement of arterial blood pressure, respectively. A cannula for recording pleural pressure was introduced into the right pleural cavity. The animals were then placed in a stereotaxic frame. The dorsal surface of the medulla was exposed by occipital craniotomy and partial cerebellectomy was performed. Electroneurograms of the right C5 root of the phrenic nerve (Phr) and the left L1 lumbar nerve (Lumb) were recorded by bipolar silver electrodes. In some cases, electromyographic activities of the sternal part of the diaphragm (Diaph) and abdominal (rectus or external obliquus) muscles (Abd) were recorded with bipolar needle and teflon-coated stainless steel wire electrodes, respectively. In three cats the electroneurogram of the right or left recurrent laryngeal nerve (Rec) was also recorded. The electrical activities were amplified, filtered, displayed on an oscilloscope (Tektronix, type 5223) and recorded together with blood and pleural pressure signals on-line at a sampling rate of 2 kHz using a computer (Pentium 133 MHz, 64 MB), equipped with the Lab View software (National Instruments). TB- and LPh-coughs, AR and ER were elicited by mechanical stimulation of the tracheobronchial, laryngopharyngeal, nasopharyngeal and glottal regions with a nylon fibre (diameter 0.3–0.5 mm). Arterial blood samples were periodically analyzed for PO_2, PCO_2 and pH using a blood gas analyser (AVL-Compact 2). Metabolic acidosis, when present, was corrected by an intravenous administration of 8.4 % sodium bicarbonate.

During *rebreathing*, end-tidal CO_2 ($ETCO_2$) was measured in a closed breathing circuit, consisting of a tracheal cannula and a small rubber balloon filled with room air, by a capnograph (Capnogard, Novametrix, USA). The rebreathing manoeuvre was terminated after 2–3 min when end-tidal CO_2 reached 8 %. In some cases, expiratory motor activity during eupnoea was provoked by short-lasting expiratory tracheal occlusion. Rectal temperature was maintained at 36–37 °C by radiant heat. At the end of the experiment, animals were killed by an overdose of pentobarbital. Medullary midline lesions were made by microinjections (0.2–0.3 μl) of excitotoxin – kainic acid (Sigma, 2 mg/ml) dissolved in phosphate buffered saline (pH = 7.4), using a 10 μl Hamilton syringe with a 33-gauge needle, mounted in a stereotaxic manipulator. Two injections were made in one track – 2.5 and 1.5 mm below the dorsal surface of the medulla, at the midline level, 2.0 mm rostral to the obex. In three cats, additional two midline injections were made in a second track at the same depths, 3.0 mm rostral to the obex. The injection solution was

saturated with Fast Green as a guide for estimating the spread of the solution. Kainic acid as an excitatory L-glutamic acid agonist produces functional inactivation of cell bodies within 30 min while sparing nerve fibres (Coyle *et al.* 1978). Therefore, we waited 30–40 min after the injections before testing their effects.

After completing the experiment, the brain stem was removed for histological processing, using sections 100 μm thick. Histological verification of lesioned sites in the medulla (Berman 1968) proved the spreading of injected solutions mostly between 0–4 mm rostral to the obex. The lesions affected mainly the areas of the obscurus and pallidus raphe nuclei and adjacent parts of the medial reticular formation, 0.5–1.0 mm bilaterally to the midline (Fig. 1).

Computer-assisted processing of the above mentioned recorded signals was performed. Under conditions of eupnoea, the respiratory frequency and the neural timing of inspiratory, post-inspiratory and expiratory phases were derived from the duration of raw Phr or Abd electrical activities or from their integrals (Richter and Ballantyne 1983). Similarly, the inspiratory and expiratory durations in provoked reflexes were evaluated from corresponding raw neural and muscle activities. The intensity of eupnoeic inspiration and expiration as well as the inspiratory and/or expiratory efforts of particular reflexes were assessed from the maximal inspiratory and expiratory pleural pressure values. The results are expressed as means ± S.E.M. Analysis of variance (ANOVA) or Student's t-test were used to determine the statistical significance of the differences, as appropriate. $P<0.05$ was considered as significant.

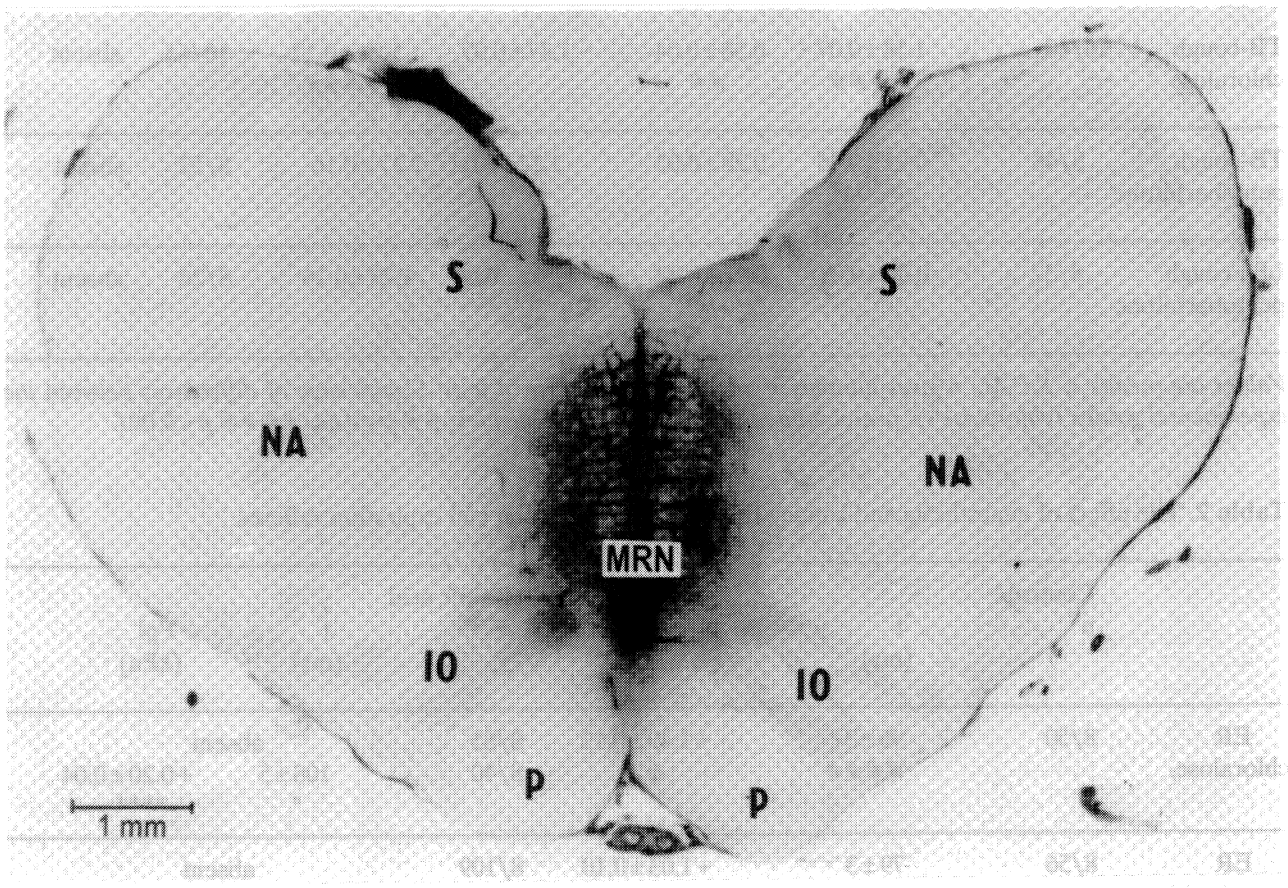

Fig. 1. *Transverse medullary section at the level of 2.6 mm rostral to the obex showing the extent of the kainic acid lesion. Abbreviations: P – pyramidal tract, IO – inferior olivae, MRN – midline raphe nuclei, S – solitary tract, NA – nucleus ambiguus.*

Results

Airway reflexes and anaesthesia

Both the neural inspiratory and expiratory durations of TB-cough were significantly longer ($p<0.001$, $p<0.02$, respectively) under chloralose anaesthesia and the maximal expiratory pleural pressures were lower ($p<0.001$), compared to the values of TB-cough in pentobarbitone-anaesthetized cats (Table 1). Similar differences in duration of expiration were determined in ER evoked in cats under chloralose vs. pentobarbitone anaesthesia ($p<0.001$,

Table 2). However, the maximal expiratory pleural pressure values during ER were higher in chloralose ($p<0.05$) compared to the pentobarbitone anaesthesia. Neural duration of AR showed no change apart from the decrease in maximal inspiratory effort ($p<0.001$) in cats under chloralose compared to pentobarbitone anaesthesia (Table 2).

Effects of midline kainic acid injections

Cough reflex

Mechanical stimulation of the tracheobronchial or the laryngopharyngeal mucosae during control breathing regularly evoked the cough reflex. It consisted of strong prolonged burst in the phrenic motoneurone discharge, resulting in a negative wave of pleural pressure which was immediately followed, or partially overlapped, by a burst in the lumbar neurogram accompanied by a strong positive deflection of pleural pressure (Fig. 2).

Table 1. Mean values of neural inspiratory and expiratory durations (t_I, t_E), maximal inspiratory and expiratory pleural pressures (P_{plI}, P_{plE}), of tracheobronchial (TB) and laryngopharyngeal (LPh) coughs in animals under chloralose or pentobarbitone in control and after kainic acid injections.

	Control n	t_I (s)	t_E (s)	P_{plI} (kPa)	P_{plE} (Pa)	Kainic acid n	
TB-cough chloralose	10/40	1.58±0.07 ####	0.38±0.04 ##	−1.37±0.07	1.24±0.17 ####	10/65	absent
TB-cough pentobarbitone	8/48	0.91±0.05	0.28±0.02	−1.22±0.06	2.17±0.16	8/52	absent
LPh cough pentobarbitone	8/32	0.92±0.03	0.22±0.02	−1.52±0.06	1.70±0.24	8/26	absent

Values are means ± S.E.M., n gives number of animals and number of tests. Significance of differences between the experimental groups (chloralose vs. pentobarbitone) is given below the figures: ## $p<0.02$, #### $p<0.001$.

Table 2. The effect of anaesthesia and kainic acid lesions on aspiration and expiration reflexes.

	Control n	t (ms)	Ppl (kPa)	Kainic acid n	t (ms)	Ppl (kPa)
ER chloralose	8/50	96±3 ####	+1.49±0.12 #	8/85 8/40	absent 108±5 *	 +0.20±0.04 ****
ER pentobarbitone	8/56	79±3	+1.03±0.10	8/109	absent	
AR chloralose	10/60	74±3	−2.01±0.09 ####	10/40	83±4 *	−1.30±0.08 ****###
AR pentobarbitone	8/56	67±2	−2.61±0.12	8/56	77±4 *	−1.96±0.11 ****

*# $p<0.05$, #### $p<0.001$ for pentobarbitone vs. chloralose anaesthesia. * $p<0.05$, **** $p<0.001$ for kainic acid blockade compared to control conditions in each anaesthetic state.*

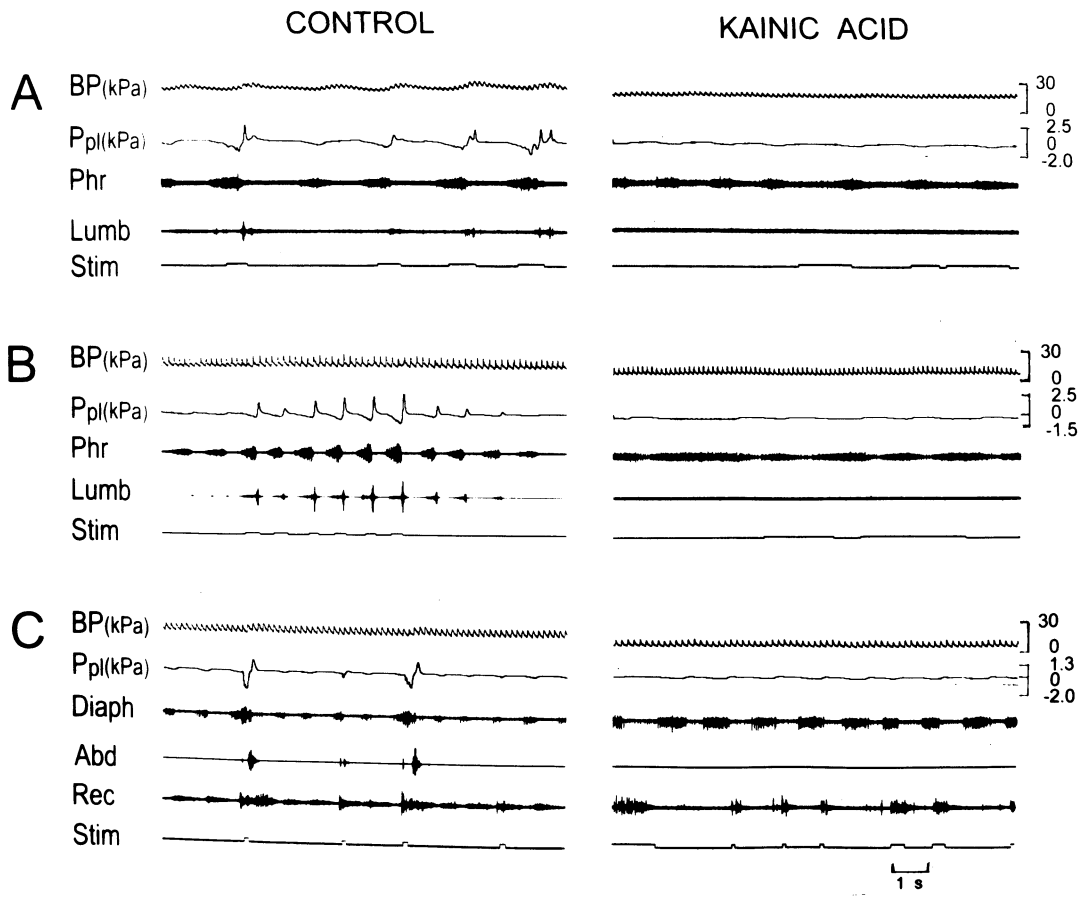

Fig. 2. *Tracheobronchial cough in cats under chloralose (A) and pentobarbitone (B) and laryngopharyngeal cough under pentobarbitone anaesthesia (C) in CONTROL condition and after KAINIC ACID injections. BP – arterial blood pressure, P_{pl} – pleural pressure, Phr – electroneurogram of the phrenic nerve, Diaph – electromyogram of the diaphragm, Lumb – electroneurogram of the lumbar nerve, Abd – electromyogram of the obliquus abdominis muscle or Rec – electroneurogram of the recurrent laryngeal nerve. Stim indicates the mechanical stimulation.*

The kainic acid injections regularly abolished both the inspiratory and expiratory signs of TB-cough in all tested animals under chloralose (Fig. 2A) or pentobarbitone anaesthesia (Fig. 2B). There was no residual phrenic and lumbar nerve (abdominal muscle) electrical activities or pleural pressure alterations resembling the cough reflex. Similarly, such injections abolished signs of the LPh cough in cats under pentobarbitone. Nevertheless, following the kainic acid injections, the electrical activity provoked by mechanical laryngopharyngeal stimulation was permanently present in the electroneurogram of Rec, while those in Diaph and Abd were regularly abolished (Fig. 2C, Table 1). The response of laryngeal motoneurons was also seen after mechanical stimulation of the tracheobronchial mucosa and the glottal region.

Expiration reflex from the vocal folds

Mechanical stimulation of the vocal folds during quiet expiration or inspiration evoked a typical ER characterized by brief forceful expiratory effort with a short burst of electrical activity in the lumbar nerves (or abdominal muscle) and by a prompt and a large positive wave in pleural pressure, without preceding inspiration (Fig. 3A, 3B). Following the kainic acid injections, mechanical stimulation failed to evoke any signs of ER in 68 % of stimulations in cats under chloralose and in all stimulations in cats under pentobarbitone anaesthesia (Fig. 3B). However, under conditions of chloralose anaesthesia, the ER still persisted in 32 % of stimulations with 87 % decrease in maximal pleural pressure values, compared to the pre-injection state (Fig. 3A, Table 2).

Aspiration reflex from the nasopharynx

Mechanical stimulation of the naso- and oropharynx *via* a small ventrolateral pharyngostomy during control inspiration or expiration regularly evoked a sniff-like (gasp-like) aspiration reflex. It was characterized by a brief, but large burst of electrical activity in the phrenic nerve (or in the diaphragm) with

a short, steep and strong negative deflection of pleural pressure (Fig. 3C). Kainic acid injections were unable to abolish the signs of AR. Nevertheless, they prolonged the duration of AR ($p<0.05$) and lowered the negativity of maximal pleural pressure values ($p<0.001$) in all animals under both types of anaesthesia (Table 2). This moderate attenuation by 35 % and 25 % of the AR after kainic acid injection was much weaker than the depression of ER.

Breathing pattern and systemic blood pressure

Pre-injection control breathing acquired two different patterns in relation to the particular anaesthetic condition. Lower frequency of breathing, with longer inspiratory, post-inspiratory and expiratory time durations and with a greater negativity of inspiratory pleural pressure values were observed under chloralose, compared to the corresponding parameters under pentobarbitone anaesthesia (Table 3). Under both types of anaesthesia, kainic acid injections only altered the frequency of breathing and the maximal inspiratory pleural pressures non-significantly. The inspiratory duration was either shortened (chloralose) or prolonged (pentobarbital), the post-inspiratory duration increased and the expiratory duration was shorter (pentobarbitone), the maximal expiratory pleural pressure values increased (pentobarbitone) or did not change (chloralose). In spite of these differences, the evaluation of arterial blood gas tensions revealed no significant changes in PaO_2 and $PaCO_2$ before and after kainic acid injections. They remained within normal limits throughout the experiments under both anaesthetic conditions. However, the lowering of pH values was corrected throughout the experiments. The expiratory motoneuronal and muscle activity provoked by hypercapnia (rebreathing, $ETCO_2$ = 8 %) or expiratory tracheal occlusion was regularly abolished by the kainic acid injections. The lesions were also accompanied by a consistent drop in systemic blood pressure in both groups of animals (Table 3).

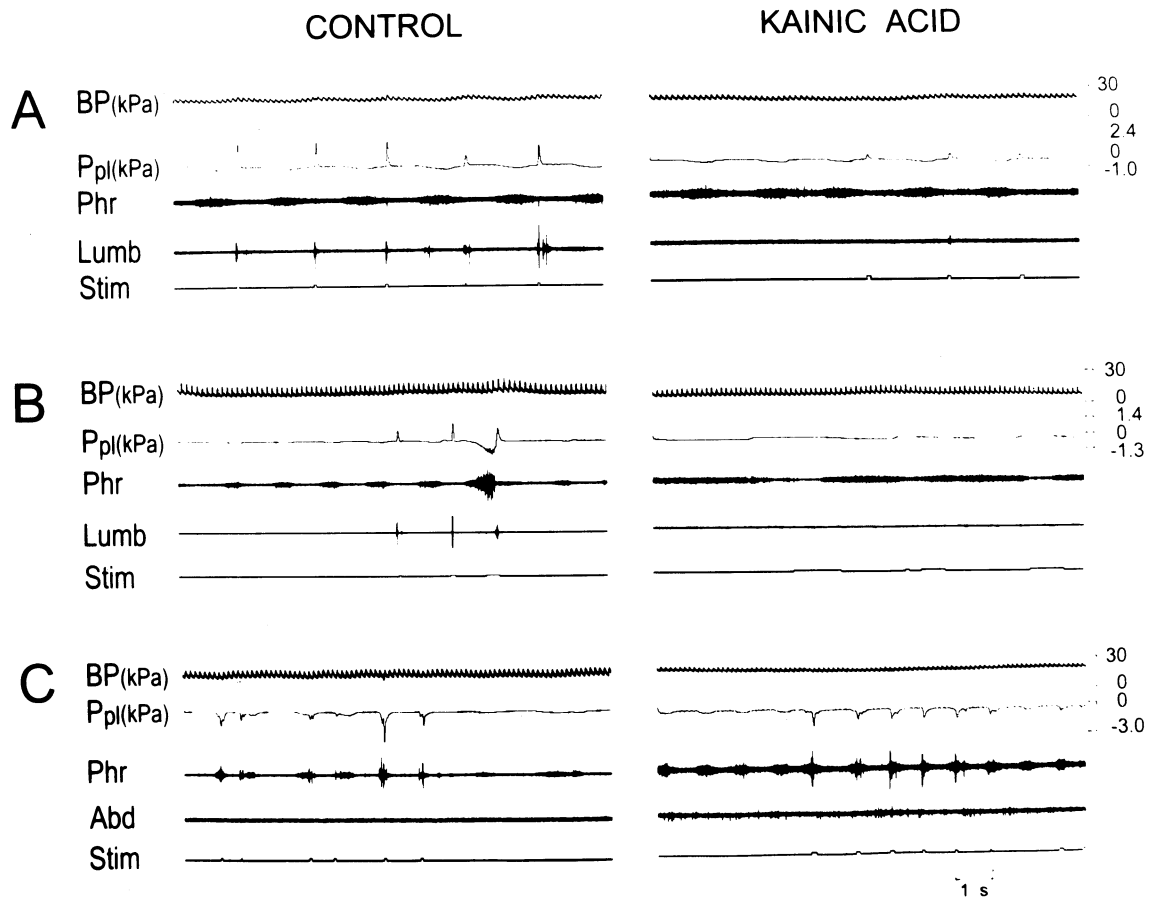

Fig. 3. *Expiration reflex in cats under chloralose (A) and pentobarbitone (B) and the aspiration reflex under pentobarbitone (C) in control conditions and after the kainic acid injections. Note two expiration reflexes followed by laryngeal cough in B. Recorded parameters as in Figure 2.*

Table 3. Mean values of respiratory rate (f), neural inspiratory (t_I), post-inspiratory (t_{E1}) and expiratory (t_{E2}) time durations, maximal inspiratory and expiratory pleural pressures (P_{plI}, P_{plE}), systolic and diastolic blood pressures (BP_s, BP_d) during eupnoeic breathing in control conditions under chloralose and pentobarbitone anaesthesia and following kainic acid blockade

	n	f (min^{-1})	t_I (s)	t_{E1} (s)	t_{E2} (s)	P_{plI} (kPa)	P_{plE} (kPa)	BP_s (kPa)	BP_d (kPa)
Chloralose									
control	10/30	12.68±0.39 ####	2.20±0.10 ####	0.70±0.05 ####	1.83±0.14 #	−0.63±0.04 ####	−0.22±0.02	26.1±0.5	17.2±0.5
kainic acid		14.23±0.88 ###	1.86±0.09 **	0.81±0.08	1.54±0.17 ####	−0.57±0.02 #	−0.27±0.02	20.4±0.7 ****	13.4±0.5 ****
Pentobarbitone									
control	8/24	19.03±0.99	1.45±0.12	0.33±0.03	1.37±0.13	−0.44±0.02	−0.19±0.01	24.5±0.8	17.5±0.6
kainic acid		18.98±1.15	1.87±0.15 *	0.71±0.08 ****	0.58±0.06 ****	−0.50±0.03	−0.25±0.02 ***	21.2±1.4 *	14.2±1.1 **

*# $p<0.05$, ### $p<0.01$, #### $p<0.001$, for pentobarbitone versus chloralose anaesthesia. * $p<0.05$, ** $p<0.02$, *** $p<0.01$, **** $p<0.001$, for kainic acid blockade compared to baseline values under chloralose and pentobarbitone*

Discussion

To our knowledge, this is the first study reporting the effect of medullary midline lesions produced by injections of the neurotoxin, kainic acid, on the cough, expiration and aspiration reflexes in anaesthetized, non-paralyzed cats. The major result concerns the finding that lesions to the obscurus and pallidus raphe nuclei and to the adjacent medial reticular formation abolish the inspiratory and expiratory components of tracheobronchial and laryngo-pharyngeal coughs and especially the expiration reflex, while regularly sparing the aspiration reflex. Similar results were found in our former experiments in cats with midsagittal brainstem surgical transection (Jakuš *et al.* 1987b). The absence of TB-cough and expiration reflexes and the maintenance of a weak aspiration reflex in those experiments were explained by the disruption of reticulospinal pathways and interconnections between the structures of both halves of the medulla located between the levels 2 mm caudal and 3 mm rostral to the obex, probably involved in these reflexes. The resemblance with our present findings after selective destruction of neuronal bodies in the medullary midline by kainic acid suggests that, apart from the fibre tracts, the raphe and medial reticular neurons are also involved in neural processing of cough and expiration reflexes. The brainstem contains several regions that are important for mediating the cough, ER and AR, including the main brainstem respiratory-related regions (the dorsal, ventral and pontine respiratory groups), the lateral tegmental field and the lateral reticular nuclei (Dyachenko 1990, Oku *et al.* 1994, Grélot and Bianchi 1996, Shannon *et al.* 1996, Jakuš *et al.* 1996, Gestreau *et al.* 1997). The lack of cough and expiration reflexes following midline kainic acid injections may be due to removal of an important source of facilitatory input to spinal respiratory motoneurons (Holtman *et al.* 1986, Dobbins and Feldman 1994, Budziňska and Romaniuk 1995) and/or to brainstem regions that could mediate cough and ER. However, the first premise seems to be more probable, because the kainic acid injections did not abolish activity of the cough and ER in the recurrent laryngeal nerve. The same mechanisms by which the kainic acid lesions may abolish the ventilatory signs of "fictive" vomiting were recently suggested by Miller *et al.* (1996). On the other hand, the kainic acid injections did not affect the AR from the nasopharynx in our experiments. Therefore, it seems that other structures located either more rostrally in the midline at the ponto-medullary junction (Jakuš *et al.* 1987b) or those located in the lateral tegmental field (Fung *et al.* 1994, 1995) could be critical for the appearance of AR.

Furthermore, kainic acid injections abolished the expiratory abdominal activity provoked by hypercapnia or by expiratory tracheal occlusion. Thus, the obscurus and pallidus raphe nuclei and the adjacent medial reticular formation may be linked to the brainstem or spinal neuronal circuitries, which are responsible for generation and/or transmission of additional expiratory drive to spinal motoneurons during enhanced breathing. However, in this study we did not record the electrical activity of neurons described in the medullary midline areas with apparent modulatory effects on cough reflex (Shannon *et al.* 1996) or the breathing pattern (Lindsey *et al.* 1992, Hosogai *et al.* 1993). Since we have not evaluated their anatomical or functional connections already reported by Holtman *et al.* (1984), Onai and Miura (1986), Miller *et al.* (1989), it was not possible to establish whether the effects of the lesions are due to the dysfunction of the respiratory or non-respiratory neurons at the medullary midline or to judge which of the above mentioned levels was actually affected. Nevertheless, the present study indicates that the midline raphe region provides an important source of the facilitatory input for inducing cough and ER.

The excitability and intensity of defensive airway reflexes, as well as the breathing pattern itself, are strongly influenced by the type and level of anaesthesia (Karczewski 1973, Korpáš and Tomori 1979). This was also corroborated in the present study, although a reasonable explanation is rather vague. It could be related to the distinctive action of the anaesthetics at various levels of the central nervous system (Roth 1980). The functions of the brainstem reticular formation responsible for basal respiratory rhythmogenesis, or for neural processing of various cardio-respiratory, laryngeal, vasomotor and spino-bulbo-spinal reflexes, are greatly attenuated or abolished by local or systemic administration of pentobarbitone (Ngai 1960, Gautier 1986, Pavlásek and Hricovíny 1984). On the other hand, the anaesthetic effect of chloralose is linked preferentially to suprapontine, especially to cortical structures (Simamura *et al.* 1968). However, it is possible that the applied dose of 55 mg/kg of i.v. chloralose does not completely remove the strong inhibitory effect of the descending reticular system on neurons mediating the cough and other polysynaptic reflexes, resulting in their depression. The systemic administration of pentobarbitone in the dose 40 mg/kg, probably totally suppresses reticular inhibition, enabling some facilitation of these reflexes. Such an explanation is in agreement with the former findings of Frank and Ohta (1971) described at the spinal level after a selective blockade of the reticulospinal inhibitory pathway by the above mentioned anaesthetic agents. In addition, chloralose anaesthesia strongly prolongs both the inspiratory and expiratory durations during eupnoeic breathing (Bianchi and Barillot 1978). Our results also seem to be relevant in connection with the timing of

expulsive processes such as the cough and ER in cats under chloralose anaesthesia. However, following the kainic acid injection the absence of cough and ER was observed in our cats under both chloralose and pentobarbitone anaesthesia. Evidently, the type of anaesthesia was not the main factor in this respect.

Furthermore, this study indicates that there is some involvement of raphe and other medullary midline structures in the formation of the neural pattern of breathing and sympathetic outflow. The kainic acid injections in our experiments did not produce any consistent changes in the frequency and depth of the inspiratory phase of breathing in cats of either experimental group. In pentobarbitone-anaesthetized cat, the application of kainic acid significantly prolonged the inspiratory and post-inspiratory time duration while it decreased the expiratory ones. Under chloralose anaesthesia, inspiration was shorter. These differences could again be related to the specific effects of anaesthetics on the respiratory rhythm generator. Nevertheless, a similar diversity in breathing patterns in response to lesions or stimulation of the medullary midline have been reported by many authors. It was shown that kainic acid lesions of neurons at the midline of the pontomedullary junction increased the respiratory frequency in decerebrate and paralysed cats (Bennett and St. John 1985). No data are available upon the respiratory effects of kainic acid lesions to the more caudal regions of the medullary midline. Electrical or chemical stimulations of serotonin-containing raphe nuclei may either inhibit (Sessle *et al.* 1981, Aoki *et al.* 1989, Lalley *et al.* 1997) or enhance (Millhorn 1986, Holtman *et al.* 1987, Morris *et al.* 1996) respiratory activity. Some novel reports also suggest the existence of assemblies of synchronously discharging respiratory-related neurons at the medullary midline regions, which could contribute to the stability of the breathing pattern (Romaniuk and Bruce 1991, Lindsey *et al.* 1992) and help to sustain the level of tonic sympathetic activity in cardiovascular regulation (Lindsey *et al.* 1991, Gilbey *et al.* 1995). Indeed, the kainic acid injections in our experiments led to a consistent fall of both systolic and diastolic systemic blood pressures in cats of both experimental groups.

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