ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol. Exp. 1997, 57: 31-39

Involvement of the motor trigeminal nucleus in respiratory phase-switching in the cat

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Abstract. We investigated the hypothesis that the motor trigeminal nucleus, consisting of expiratory motoneurons, might be influential in termination of inspiration. We addressed the issue by comparing the effects on neural respiration of a reversible, unilateral, pharmacologic blockade of the motor trigeminal nucleus (5M), the medial parabrachial nucleus (PB), and of other nearby structures that are neutral for respiration in anesthetized, vagotomized, paralyzed, and ventilated cats. The blockade was achieved by microinjections of 2% xylocaine, laced with Pontamine Sky Blue to identify sites of injections, from the tip of a penetrating microelectrode. Integrated phrenic neurograms were recorded to quantify the time of neural inspiration (T_I), expiration (T_E), and the peak phrenic amplitude. We found that blockade of the 5M caused a pattern of apneustic respiration, consisting of a selective prolongation of inspiratory phases that were interrupted by short expiratory pauses. In contrast, blockade of the PB resulted in a prolongation of both T_I and T_E, which corresponds to a mere slowing of respiration. The results confirmed important functions of the rostral pons in ventilatory control but pointed to the 5M rather than PB as a structure underlying the inspiratory off-switch. We conclude that the motor trigeminal nucleus may have a part in the pontine pneumotaxic mechanism.

Key words: apneustic respiration, cat, motor trigeminal nucleus, parabrachial-Kölliker-Fuse complex, pneumotaxic mechanism, pons, respiration

INTRODUCTION

The motor trigeminal nucleus (5M) has until recently been thought of as a cluster of motoneurons engaged, among other things, in maintaining the upper airway patency (St. John 1987, Kukwa et al. 1989). The nucleus has not been positively associated with the regulation of the pontine respiratory phase-switching. This notion has been recently challenged by Gromysz et al. (1988, 1990a) who found that the 5M consists mostly of expiratory neurons and have shown evidence implicating it in the pneumotaxic mechanism in the rabbit. The evidence is based on 5M removal and stimulation experiments. Removal delays the inspiratory off-switch leading to a prolongation of the inspiratory time (T_I). This prolongation assumes an apneustic pattern when the vagi are severed. Conversely, stimulation facilitates the inspiratory off-switch. The evidence is further substantiated by an apparent relaying of vagal inflation-deflation reflexes at the 5M, since these reflexes are abolished after 5M removal (Gromysz et al. 1990a). The latter is in contrast to the lesions of the hitherto considered most likely locus of the pneumotaxic mechanism, the nucleus parabrachialis medialis (PB) and Kölliker-Fuse nucleus, referred to in this work as the parabrachial complex. Such lesions do not eliminate these reflexes (Feldman and Gautier 1976).

The possible involvement of the 5M in ventilatory control gained further support in recent studies by Fung and St. John (1994a) in the cat. They reported a spectrum of regions rostral, caudal, and medial to the PB complex, the 5M among others, that were involved with pontine ventilatory control. Moreover, different aspects of neural respiration may be regulated by separate regions. Neurons in the rostrolateral tegmentum at the ponto-mesencephalic border seem to control the duration of neural inspiration (Fung and St. John 1994b).

Since the specificity or its lack of any one group of neurons in the rostral pons in termination of inspiration is critical for an understanding of the off-switch mechanism, we thought it warranted further scrutiny of the suggested respiratory role of the 5M in the cat. We addressed the issue by comparing the effects on neural respiration of a reversible, unilateral, pharmacologic removal of the function of the 5M, the PB, and of other nearby structures of no known respiratory role as a basic control. We hypothesized that such a comparison would enable us to pinpoint the functional differences of various structures in regard to the off-switch effect. We found that the blockade of the 5M, unlike that of the PB, produced prolonged inspiratory holdings of the apneustic type. The study suggests that the motor trigeminal nucleus has to do with the inspiratory off--switch in the cat.

METHODS

The experiments were done on 20 adult cats of either sex, weighing 2.6-3.5 kg, anesthetized with Nembutal (35 mg/kg body wt, i.p.). The cats were divided into four groups. Three groups were given a unilateral, on the left side, xylocaine blockade (see details below) in the upper pons. These groups differed by the neural area blocked. In the first group (9 cats) the blockade was performed in the 5M, in the second (4 cats) in the PB, and in the third (4 cats) outside the two aforementioned areas. The latter were the nearby pontine reticular formation in three cases and the facial nerve fiber tract in one. The third group served as overall control for the other two. The fourth group consisted of three cats that received identical applications of 0.9% saline in either the 5M (2 cases) or PB (1 case). Each animal was used for one area block once to avoid undue contaminations of later histologic preparations by dye traces or microelectrode channels.

Surgical procedure

The cats were placed in the prone position, tracheostomized, paralyzed with pancuronium bromide (Pavulon, 0.1 mg/kg/h) and mechanically ventilated with room air. Both vagus nerves were isolated and transected in the mid-neck. A right C_5 root of the phrenic nerve (contralateral to the neural blockade) was exposed, transected, desheathed, and placed on bipolar silver recording electrodes. The dorsal brain stem surface was exposed by an occipital craniotomy and a portion of the cerebellum caudal to the posterior colliculi removed by suction. The cerebellar space was filled with agar to minimize movement artifacts. The preparation included cannulations of the femoral artery and vein. The anesthetic was supplemented (5 mg/kg body wt iv) when there were signs of waning of anesthesia, like irregular fast neural respiration or if blood pressure and heart rate increased either spontaneously or in response to noxious stimuli by more than 10% with respect to the control values obtained at the beginning of the experiment. Rectal temperature was maintained at ~38°C.

Technique of neural blockade

We used a technique of blockade described previously by Gromysz et al. (1990a). Briefly, the glass microelectrode (tip diameter ~10 μm) was filled with a 2% solution of xylocaine laced with the dye Pontamine Sky Blue to aid subsequent histologic localization. The cat's head was mounted in a holder by putting the ear plugs into the external auditory canals and clamping the infraorbital bridges.Berman's (1968) atlas of the cat brain stem (Plate 16-18) was used as a basic stereotaxic reference with the modification of the head's angle to have the 5M positioned beside rather than beneath the PB. This modification, which would obviate the need to pierce with the microelectrode through the PB on the way down to the 5M, required us to have the pons surface facing nearly horizontally. It was ascertained that such a horizontal positioning in the cat is set when lambda is 15 mm below bregma in the sagittal plane, and therefore the head was fastened in each case at an angle required to achieve this distance. The above modification influenced the stereotaxic coordinates and made us produce our own working atlas of the brain stem. The final coordinates were based on this atlas and for insertion of the microelectrode to the 5M were: 9.5-11.7 mm rostral to the obex, 3.0-4.0 mm lateral to the midline, and 0.8-2.2 mm below the bottom surface of the IVth ventricle. The respective coordinates for the PB were: 11.8-13.8 mm, 3.0-4.5 mm, and 0.0-1.5 mm. The microelectrode setting in the 5M was confirmed by recordings of neuronal activities in synchrony with the expiratory phase of the phrenic discharge and that in the PB by recording respiratory-related units. Once confirmed, the recording was stopped and ~0.5 μL xylocaine, premeasured with a Hamilton microsyringe, was pressure-extruded by hand through a syringe attached to the microelectrode. The PB was localized and blocked in a similar way in another set of cats. The control injections of ~0.5 μL laced saline caused no noticeable changes of the phrenic neurogram, indicating no disruptive effects of the injection itself.

The effectiveness of xylocaine in blocking the function of neural structures has been ascertained in a previous work (Gromysz et al. 1990a). The effects of block are expressed maximally at 3 min, start abating at 10-15 min, and fully revert after 30 min. This method has an advantage of producing fairly rapid and reversible effects and enables comparisons of normal and changed respiration in the same animal.

Recording procedures

The microelectrode used allowed satisfactory, albeit noisy at times, recording of the extracellular neuronal activity. This activity, not shown in the paper as it served basically to confirm the localization of a nucleus, and that of the phrenic nerve were amplified, filtered, and integrated with a time constant of 100 ms (Digitimer - Neurolog System). End-tidal fractional concentration of CO_2 ($F_{ET}CO_2$) (Engstrom Eliza analyzer) and arterial blood pressure were continuously monitored and maintained within a normal range. All these recordings were displayed on a strip-chart hot-stylus polygraph (Honeywell - Omnilight 8M36). The animal's condition during the experiment was additionally monitored as required by the measurements of the acid-base balance and arterial blood gas content (Ciba Corning 238).

The experiments ended with a perfusion of the brain with a 4% formaldehyde solution. The brain stem was removed and stored for histologic examination performed at a later time on serial, frozen, transverse sections of 50 μm thickness. The sites with clearly grouped dye traces were taken as reflecting the microelectrode tip's position. The experiments in which no traces could be found were disregarded.

Measurements and data analysis

We defined the apneustic pattern of breathing in accordance with Lumsden's (1923) original description, i.e., as an extensive prolongation of T_I with little changes of T_E, resulting in long inspiratory holdings interrupted by short expirations. Coherent with this definition is an undisputable increase of the T_I/T_E ratio.

From the phrenic neurogram, the following variables were measured and quantified: duration of the activity from its onset to peak (neural inspiration, T_I), duration to the next onset of the activity, (neural expiration, T_E), and peak amplitude. The T_I/T_E ratio was calculated.

The mean value of each variable was computed from 3 full respiratory cycles before and at 3 min after the blockade. Data are expressed as means ± SE. Comparisons of the corresponding pre- and post-blockade means within each group were made with a paired *t*-test. An unpaired *t*-test was employed for comparing the T_I and T_E in a group. Comparisons of the effects on a given variable of the blockade across the three pontine structures studied were made with a one-way analysis of variance (ANOVA) for repeated measurements fol-

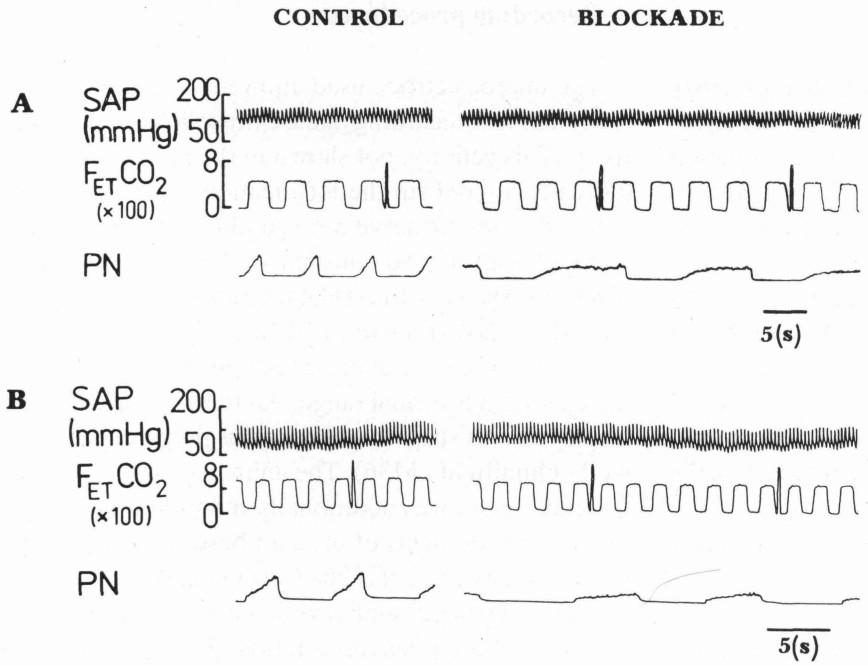

Fig. 1. Original recordings showing the effects of xylocaine blockade performed in the region of the motor trigeminal nucleus (Panel A) and the medial parabrachial nucleus (Panel B) in separate cats. Traces from top in each panel are: systemic arterial pressure (SAP), end-tidal fractional concentration of CO_2 ($F_{ET}CO_2$), and phrenic neurogram (PN). High spikes on the CO_2 traces are repeat automatic calibrations corresponding to $F_{ET}CO_2$ 0.08. The blockade produced a prolongation of T_I in A (apneustic respiration) and of both T_I and T_E in B (slow respiration).

lowed by the Scheffe *post hoc* test. $P<0.05$ was considered as significant.

RESULTS

Figure 1 shows representative recordings before and after the blockade of the 5M and the PB in separate cats. The 5M blockade (Panel A) resulted in a 4-fold prolongation of T_I with nearly unchanged T_E, leading to the apneustic pattern of respiration in an otherwise stable preparation. The PB blockade (Panel B) caused a mean 1.6-fold prolongation of both T_I and T_E, which amounted to the slowing of respiration. Delayed termination of the phrenic discharge was accompanied by the diminution

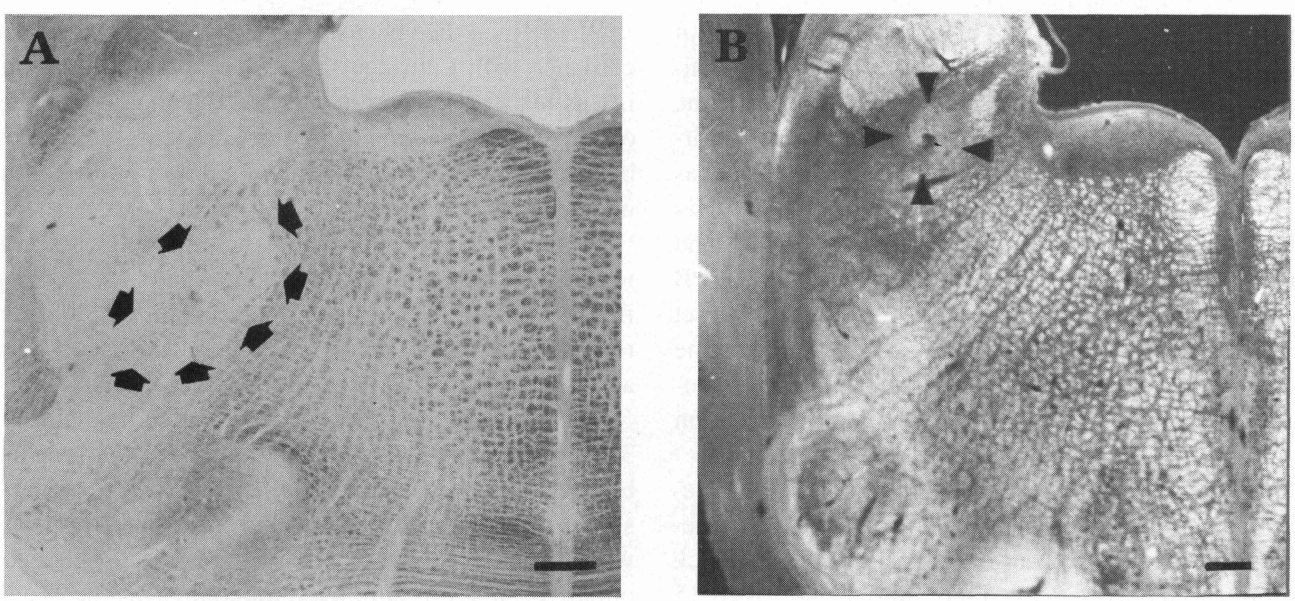

Fig. 2. Photomicrographs of transverse sections showing the sites of blockade whose effects are displayed in Fig. 1; A, the motor trigeminal nucleus, sectioned 10.0 mm rostrally to the obex and B, the medial parabrachial nucleus, sectioned 11.8 mm rostrally to the obex. The groove running vertically along the right margin of the photomicrograph is the midline. The dye and/or microelectrode channel traces are in the center of the areas outlined by arrows in each. Bar, 500 μm in each.

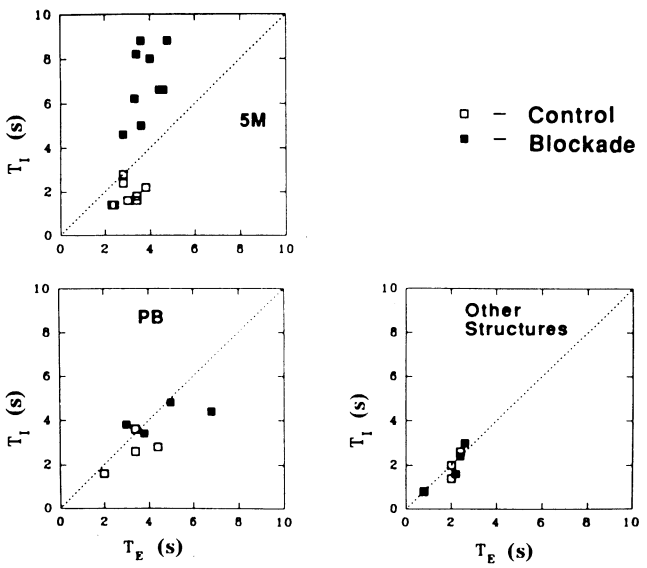

Fig. 3. Relationship between the duration of neural inspiration (T_I) and expiration (T_E) in individual cats before (open squares) and after (closed squares) xylocaine blockade of the motor trigeminal nucleus (5M), the medial parabrachial nucleus (PB), and other structures. Diagonal dashed lines are identity lines. Note a dominant lengthening of T_I after 5M blockade, contrary to that after PB blockade where both T_I and T_E were lengthened.

of its peak height in either case. Figure 2 demonstrates histologic confirmation of the blockade sites being in the 5M (Panel A) and the PB (Panel B) of the respective cats.

A contrasting comparison of the individual changes of T_I and T_E evoked by xylocaine blockades in the three areas of the pons studied is shown in Fig. 3. Blockade of the 5M caused a marked prolongation of T_I, which was in each case manyfold greater than the accompanying small lengthening of T_E. In contrast, blockade of the PB caused only modest and comparable increases of both T_I and T_E. The blockade effects of the other structures were virtually nil. The corresponding mean numerical data of T_I and T_E before and after the blockade in the three areas are given in Table I. Significant prolongations of T_I due to the blockade were noted in both 5M and PB groups ($P<0.05$; t-test). The T_I increase averaged 5.02 ± 0.44 s (range 3.0-6.6 s) in the 5M group and was much greater than either the 1.45 ± 0.30 s (range 0.8-2.2 s) increase in the PB group or the 0.25 ± 0.11 s (range 0.0-0.4 s) change in the other structures group ($P<0.01$; ANOVA and the Scheffe test). In the 5M group, as opposed to the other groups, the T_I increase was also strikingly greater ($P<0.001$; t-test) than the concomitant T_E lengthening of 0.87 ± 0.21 s (range 0.2-2.1 s). This prolongation of T_E did not differ significantly from that in the PB group, which amounted to 1.38 ± 0.41 s (range 0.5-2.4 s).

The predominant prolongation of T_I after 5M blockade caused the T_I/T_E ratio to increase by an average of 1.17 ± 0.10, i.e., by 174% ($P<0.001$; t-test). A significant difference was noted in the post-blockade ratio across the three groups; the source of the difference being the increase in the 5M group ($P<0.01$; ANOVA and the Scheffe test). The ratio changed inappreciably in the other two groups (Fig. 4).

The marked prolongation of T_I in the 5M but not PB group notwithstanding, a common feature of the blockade in both areas was a decline of the peak phrenic amplitude (Fig. 5). There was no significant difference between the reduced phrenic amplitude in the 5M and PB groups, but either was different at the 0.01 level from that

TABLE I

Changes in neural inspiration (T_I) and expiration (T_E) in response to xylocaine blockade of the motor trigeminal nucleus (5M), the medial parabrachial nucleus (PB), and other structures

	5M $n=9$		PB $n=4$		Other Structures $n=4$	
	Control	Blockade	Control	Blockade	Control	Blockade
T_I (s)	1.96 ± 0.17	6.98 ± 0.52* **	2.65 ± 0.41	4.10 ± 0.31*	1.70 ± 0.39	1.95 ± 0.48
T_E (s)	2.97 ± 0.16	3.83 ± 0.22*	3.30 ± 0.49	4.68 ± 0.82*	1.80 ± 0.35	2.00 ± 0.41

Values are means ± SE. *$P<0.05$ vs. control in each group (paired t-test); **$P<0.05$ vs. PB and other structures (one-way analysis of variance ANOVA and the Scheffe *post hoc* test).

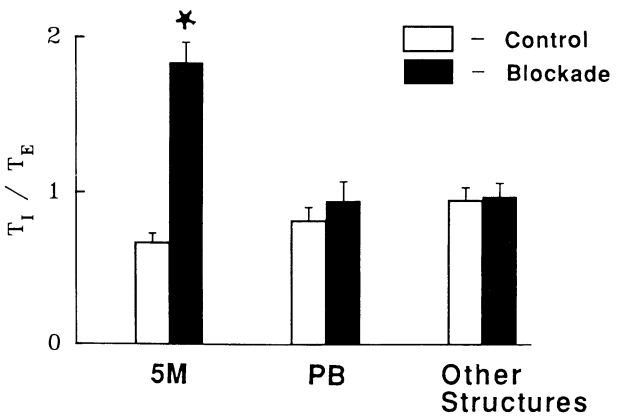

Fig. 4. Changes in the T_I/T_E ratio after xylocaine blockade. Only the 5M group showed a large increase in the ratio. *P<0.001 vs. the corresponding control (t-test) and <0.01 vs. the PB and other structures blockade (ANOVA and the Scheffe test). No two control groups were significantly different at the 0.05 level.

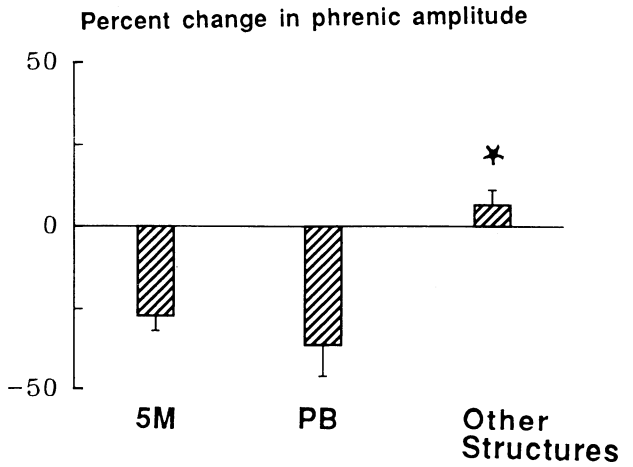

Fig. 5. Percent change in peak phrenic amplitude from control after xylocaine blockade in the three areas studied. *P<0.01 vs. PB and 5M (ANOVA and the Scheffe test).

of the other structures (ANOVA and the Scheffe test), which was not changed appreciably by the blockade.

Since comparisons of absolute values of changes of T_I and T_E among various groups could be misleading due to differences in control levels, these data were normalized by expressing them as percentage changes from control. The percent increases of T_I and T_E due to xylocaine blockade of the three areas are compared in the left and right panel of Fig. 6, respectively. This comparison gives a similar outcome to that performed on the absolute values. Note that the 266% increase of T_I after 5M blockade was much larger (P<0.001; ANOVA and the Scheffe test) than the small increases of 65% and 12% after PB and other structures blockade, respectively. The latter and also the small changes of T_E were not different from one another.

DISCUSSION

The main observation of the study was that the blockade of the motor trigeminal nucleus advanced the phrenic discharge and made its termination delay, lead-

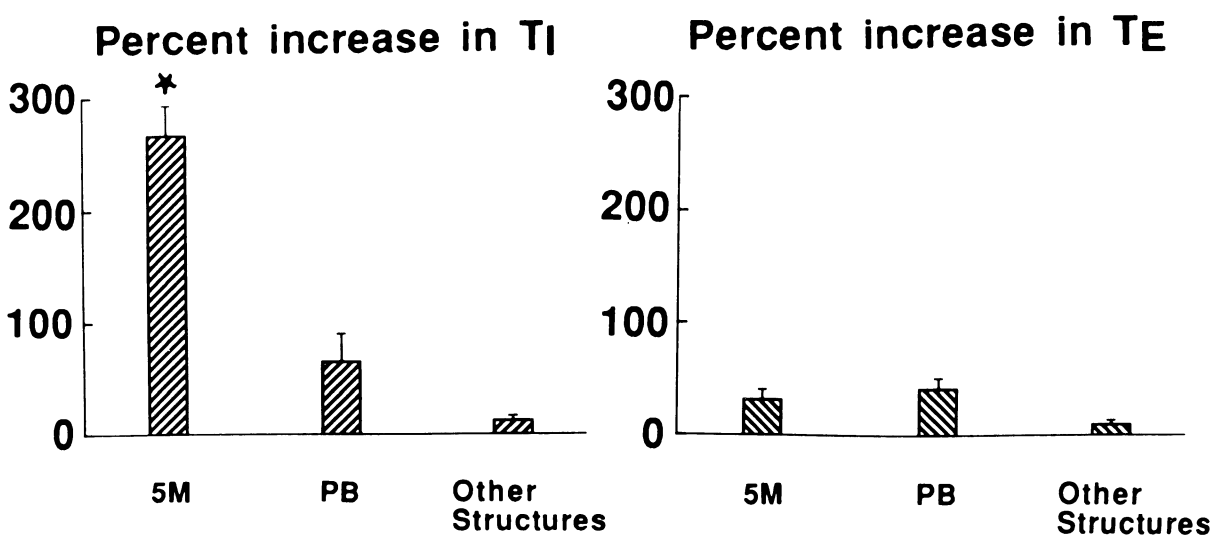

Fig. 6. Percent increases in T_I and T_E from control after xylocaine blockade in the three areas studied. Note impressive lengthening of T_I after 5M blockade, contrasting with other lackluster changes. *P<0.001 vs. PB and other structures (ANOVA and the Scheffe test). There were no significant differences noted between other groups.

ing to an apneustic pattern of breathing. The corollary is that the neural elements of this area are operational in shaping the inspiratory off-switch.

As far as we know the information about the 5M as being influential in the central control of ventilation is sparse. The 5M is made up of expiratory neurons that send axons to the muscles engaged in the control of upper airway patency. This is typified by the mylohyoid nerve, a branch of the trigeminal nerve, whose activity is in synchrony with the expiratory phase of the central respiratory cycle and is stimulated by lung stretch receptors (Kukwa et al. 1989) and diminished during apneustic breathing (Gromysz et al. 1990b). The possibility of the 5M having an off-switch effect may be inferred from a study by St. John (1987) in which stimulation of the rostral pons caused a sustained augmentation of trigeminal nerve expiratory activity and a premature termination of inspiration. The author does not relate the two events and discounts the possibility of direct or indirect stimulation of the 5M.

The 5M is located closely caudally and ventrally to the PB complex (Berman 1968). It is therefore not improbable that the 5M involvement has not come to light in the experiments based on mid-pontine transections (Glasser and Tippett 1965), stereotaxic coordinates alone (Berger et al. 1978), various blunt focal destructive lesions (Ngai and Wang 1957, St. John et al. 1971), or equally blunt electrical stimulation (St. John 1987), all of which lead to an impaired off-switch and apneustic breathing in anesthetized and vagotomized animals. When supported by the histology, those studies show extended and blurred outlines of tissue destruction which may have encompassed the 5M.

From a functional standpoint, the assessment of T_E changes concomitant to those of T_I seems to have often been overlooked in previous studies. The T_E may not be mentioned at all (Berger et al. 1978) or not quantified (St. John et al. 1971), although in both papers it is clearly lengthened and even is at times longer than T_I (e.g. Fig. 1 of Berger et al. (1978)). The T_E lengthening, observed also by others (St. John 1979, Caille et al. 1981), does not fully agree with the definition of apneustic breathing as being one of sustained inspiratory discharges interrupted by short expirations (Lumsden 1923, Monteau et al. 1989, Pierrefiche et al. 1992). It is our notion that the simultaneous lenghtening of both T_I and T_E represents a slow respiration, which is a qualitatively different state from that of apneustic respiration. Our results showed that the blockade of the 5M selectively impaired the inspiratory off-switch with ensuing nearly tripling of the T_I/T_E ratio. Furthermore, this apneustic pattern was linked only with the removal of the 5M, as was the prolongation of both T_I and T_E with that of the PB. These distinctly different effects on neural inspiration and expiration strengthen the suggestion that the 5M is part of the off-switch mechanism.

The functional entity of the pneumotaxic mechanism seems unquestionable but the localization of the underlying neuronal structures is less certain. Arguably, these structures are in the upper pons. The exact locus has variously been identified in the locus coeruleus (Johnson and Russel 1952), the rostral tegmentum (Tang 1953), and more recently in the PB complex (Bertrand and Hugelin 1971, Cohen 1971). Using more refined techniques of chemical lesioning and electrical stimulation, Fung and St. John (1994a, b) showed recently that the loci involved with the pneumotaxic mechanism extended beyond the PB complex, rostrally to the region of the nucleus of the lateral lemniscus and caudally and ventrally to the regions of the superior vestibular and spinal trigeminal nuclei. This report and those earlier by Bassal and Bianchi (1981a, b), showing that stimulations of areas even remotely rostral with respect to the PB complex may induce respiratory phase-switching, raise the possibility that the pneumotaxic effects observed during the manipulations in the rostral pons may be nonspecific in that they would affect the fibers originating elsewhere. On the other hand, Fung and St. John (1994b) have brought the attention back to the rostral pons, separating the off--switch from on-switch functions by ascribing each to a confined area; the former to the lateral tegmentum at the ponto-mesencephalon border that regulates the length of T_I and the latter to the PB complex that regulates the T_E. In the latter case, however, in eight out of the thirteen loci in which injections of kainic acid increased T_E the prolongation of T_I was also noted. These authors also mentioned the 5M as being within the pneumotaxic bounds but with no clear function ascribed to it. The present study is in general accord with those data but points to the 5M as yet another possible area involved specifically with the T_I regulation. Our result and that of Fung and St. John (1994a, b) are seemingly at odds with that of Denavit-Saubie et al. (1980) who unilaterally injected 0.5 µL of kainic acid into the PB in the vagotomized cat and obtained an apneustic respiratory pattern. Examination of their original recordings shows, however, that T_E was also substantially increased over the control duration, albeit less so than T_I. Moreover, the dominant ef-

fect of a similar kainic acid injection in the nonvagotomized cat was a prolongation of T_E.

The PB complex does have a role in shaping the respiratory rhythmicity that goes beynd the T_E regulation. This area contributes to the lowering of the inspiratory off-switch threshold (St. John 1987). Its removal, quite the contrary to that of 5M (Gromysz et al. 1990a), does not abolish the vagal reflexes (Feldman and Gautier 1976) but increases the off-switch and on-switch thresholds, leading to a slowing of respiration. It may also play a role in shaping the tidal response, as judged from the decrease of the phrenic height observed.

There are a few issues that may limit the interpretation of this work. The spread of an injected substance into the brain depends, to a large extent, on the diffusion properties of the substance and on the brain microenvironment (Nicholson 1985) and neither has been assessed in the study. The 5M is within 0.6-1 mm of the PB (Berman 1968). With the relatively large volume of microinjections used, some spread into the neighboring area is not unlikely. For one thing, such spread could be responsible for the accompanying small changes of T_E after 5M blockade and of T_I after PB blockade; the changes that would not have taken place otherwise. On the other hand, the strikingly different effects on neural respiration of each area blockade and the dye traces confined to either area seem to contradict the possibility of any substantial spillover. Denavit-Saubie et al. (1980) reported no respiratory effects of kainic acid injections of a similar volume made as close as 0.8 mm medially of the PB, which would also speak against the possibility of a spillover. Another issue concerns the mode of action of xylocaine. The drug acts by inhibiting ionic fluxes required for initiating and conducting neuronal impulses. In addition to blocking the perikarya, the drug also blocks the conduction of axons in passage. Fibers from the parabrachial complex may potentially course through or just lateral to the 5M on their way out to the ventral respiratory group of the medulla (Denavit-Saubie et al. 1979, Bystrzycka 1980, Takeuchi et al. 1980, Smith et al. 1989). Medullary input to the pons could be affected likewise. If, however, the apneustic pattern observed were due to the blockade of fibers in passage originating in the PB, than a similar or even stronger effect of the kind would be expected from the blockade of the very somata sending out these axons, which was not the case. Unrecognized interactions with other areas are also possible. A different study design would be required to address these issues.

In conclusion, although this study does not define the exact neural determinants of the pneumotaxic mechanism, we believe we have shown that the motor trigeminal nucleus is germane to the inspiratory off-switching. The nature of the interaction of this nucleus with other pontine areas engaged in the pneumotaxic function requires further studies.

ACKNOWLEDGEMENTS

This research was funded by the statutory budget of the Polish Academy of Sciences Medical Research Center. The preparation of the manuscript was supported by the Japan Society for the Promotion of Science.

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Received 14 February 1996, accepted 20 December 1996