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ACTIVATION OF THE HUMAN DIAPHRAGM FROM THE MOTOR CORTEX

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SUMMARY

1. Rapidly conducting corticofugal pathways were activated by percutaneous electrical stimulation of the motor cortex in normal subjects. The electromyographic response produced in the diaphragm was assessed with recordings via a gastro-oesophageal catheter and the mechanical response was measured as a change in transdiaphragmatic pressure.

2. The mean latency from the cortical stimulus to the muscle action potential in the diaphragm was 12·3 ms. The latency to the diaphragm from stimulation of the cervical spinal cord at the C4 level was 8·0 ms. The mean 'central conduction time' to the phrenic motor nucleus of 4·3 ms (range 4·0–4·6 ms) was similar to that for the deltoid (mean 4·4 ms; range 4·0–4·8 ms) recorded in the same subjects.

3. The largest twitch contractions of the diaphragm were evoked by cortical stimuli near the vertex during inspiration. The amplitude and duration of the electromyographic and mechanical responses often exceeded those produced by a supramaximal stimulus to both phrenic nerves simultaneously.

4. These results provide the first direct evidence that there is a rapidly conducting oligosynaptic pathway from the motor cortex to the human diaphragm.

INTRODUCTION

There are clearly both voluntary and chemical influences on human respiration. However, few data exist about the cortical projections to respiratory muscles in man (see Nathan, 1963; Campbell, Agostoni & Newsom Davis, 1970). In the cat, single electrical stimuli to the sensorimotor cortex produce a complex series of excitatory and inhibitory events in inspiratory motoneurones. The earliest component is of short latency and does not appear to relay in ponto-medullary respiratory centres (Colle & Massion, 1958; Bassal, Bianchi & Dussardier, 1981; Lipski, Bektas & Porter, 1986). There is no comparable information in man. In their classical studies of the functional map and excitability of the human cerebral cortex Penfield and Woolsey both failed to mention an effect of motor cortex stimulation on respiratory muscles although vocalization was sometimes noted with stimulation at other sites (Penfield & Boldrey, 1937; Woolsey, Settlage, Meyer, Spencer, Hamuy & Travis, 1952; Penfield & Jasper, 1954; Woolsey, Erickson & Gilson, 1979; see also Kennard, 1949).

Given the obvious voluntary control of respiration in speech and singing, we decided to investigate the cortical projection to respiratory muscles in man using the technique of cortical stimulation introduced by Merton & Morton (1980). High-voltage stimuli applied over the motor areas of the cortex can excite rapidly conducting corticofugal pathways to spinal motoneurones. Excitation of limb muscles occurs at short latency and may be powerful enough to activate, at least in distal muscles, all the motoneurone pool (Marsden, Merton & Morton, 1981). The present study documents a powerful, rapidly conducting projection from human motor cortex to the diaphragm.

METHODS

Nine experiments were performed on three healthy subjects (including the authors) who ranged in age from 30 to 33 years. Each subject was studied on two or more occasions. They showed no signs of respiratory or neurological disease. Informed consent was obtained and the procedures used have been approved by the appropriate institutional ethics committees. Subjects were comfortably seated in an air-conditioned room throughout each experiment.

Stimulus and recording technique

Electrical stimuli from a Devices D180 stimulator were applied over the motor areas of cortex through a pair of Ag–AgCl electrodes (10 mm diameter) attached to the scalp with collodion and filled with conductive jelly. For the diaphragm the usual montage consisted of an anode at the vertex and the cathode 6–7 cm anterior to it. For muscles in the upper limb the anode was placed 5–7 cm lateral and 1 cm anterior to the vertex with the cathode at the vertex. A ring of electrodes around the perimeter of the scalp was also used as cathode in some experiments (Rossini, Marciani, Caramia, Norma & Zarola, 1985). The stimulator delivered up to 750 V via a capacitative discharge with a 50 or 100 μs time constant (for details see Merton & Morton, 1980). Using the electrode positions described above there was no obvious difference in the stimulus intensity required to activate motoneurone pools of the diaphragm or proximal muscles of the upper limb.

To estimate the 'central conduction time' from brain to spinal cord, the peripheral conduction delay was measured by using the same stimulator to activate spinal motoneurones (or the proximal portions of their axons) at segmental levels (Rossini, Stefano & Stanzione, 1985; Snooks & Swash, 1985; Mills & Murray, 1986). The cathode was positioned over the spinous process of the fourth cervical vertebra with the anode on the inion. In addition, to determine the peripheral conduction time for phrenic motor axons, unilateral or bilateral stimulation of the phrenic nerve was performed with a cathode placed posterior to the lateral border of the sternomastoid at the level of the cricoid cartilage (Sarnoff, Sarnoff & Whittenberger, 1951; McKenzie & Gandevia, 1985). The electrodes used to stimulate the phrenic nerve could be clamped in an adjustable neck brace (for details see Gandevia & McKenzie, 1985). The intensity of the stimuli to each nerve was adjusted independently to ensure that maximal compound muscle action potentials were recorded. The stimuli to the phrenic nerves consisted of rectangular pulses of 0·3 ms duration at 1·2–1·5 times the intensity required for a maximal muscle action potential.

Diaphragmatic electromyographic activity (e.m.g.) was monitored using a gastro-oesophageal catheter with the active electrode close to the level of the motor point (on the right) and the other electrode 7 cm proximal to it. Details of the properties and positioning of these recording electrodes have been published (McKenzie & Gandevia, 1985). The catheter also contained two respiratory balloons to measure gastric and pleural pressures and an additional 'stabilizing' balloon which was positioned at the level of gastro-oesophageal junction. This balloon was filled with 10–15 ml of air and a weight of 50 g placed on the external end of the catheter. The transdiaphragmatic pressure was monitored with a transducer which was linear in the range 0–200 cmH_2O and was calibrated with a water manometer. In one study e.m.g. was recorded directly from the costal diaphragm via a pair of stainless-steel (hook-wire) electrodes (50 μm diameter) which were insulated to their tip with Teflon. The interelectrode distance was approximately 1 mm. These electrodes were inserted via a 25 gauge spinal cannula in the ninth intercostal space in the anterior axillary line. In separate

studies on this and another subject inspiratory activity was recorded from the right fourth parasternal intercostal muscle with a standard concentric needle electrode. In each subject the e.m.g. responses to cortical and spinal stimulation were also monitored in the deltoid muscle with standard surface electrodes (interelectrode distance 40 mm).

To ensure that minimal latencies were measured, cortical stimuli were delivered during weak voluntary activation of the muscles under test (see Day, Dick, Marsden & Thompson, 1986). Voluntary contraction also facilitates the size of response to a cortical volley probably by increasing the excitability of spinal cord circuitry (Berardelli, Cowan, Day, Dick & Rothwell, 1985). For the diaphragm, stimuli were delivered during tidal inspiration or when a transdiaphragmatic pressure of 10–20 cmH_2O was generated by the subject with the lung volume at, or near, functional residual capacity (F.R.C.). For the deltoid, stimuli were delivered during a weak contraction of 5–10% maximum assessed by ongoing e.m.g. activity. Subjects received feed-back of the background contractions (e.m.g.) and transdiaphragmatic pressure on an oscilloscope. All e.m.g. signals were filtered (1·6 Hz–1·6 kHz), stored on tape for re-analysis, and averaged by a laboratory microprocessor with a sampling rate of 4·5 kHz. If the responses recorded with the gastro-oesophageal electrodes were contaminated by the electrocardiogram they were rejected from the averager.

Because the amplitudes of e.m.g.s recorded via a gastro-oesophageal catheter are prone to systematic artifactual changes with changes in lung volume (Gandevia & McKenzie, 1986) particular attention was taken to ensure that this factor did not influence the reported results. All scalp, spinal and peripheral stimuli designed to activate the diaphragm were delivered under closely comparable conditions and the mechanical responses produced by the stimuli were also monitored (see Figs. 2, 4 and 5).

RESULTS

Single stimuli to the scalp overlying the motor cortex activated respiratory muscles at short latency. Fig. 1 shows a sample of the intramuscular e.m.g. recordings from the costal diaphragm. The cortical stimulus delivered during a tidal inspiration activated the diaphragm at a latency of about 13 ms and was often followed by a silent period. The cortical stimuli usually produced a larger 'twitch' change in the transdiaphragmatic pressure than that produced by a bilateral supramaximal stimulus to the phrenic nerves. In some experiments the twitch produced by cortical stimulation was up to 100% larger than that produced by a bilateral supramaximal stimulus to the phrenic nerves (Fig. 1, see also Fig. 5). The changes in transdiaphragmatic pressure produced by cortical stimulation consisted predominantly of a reduction in intrapleural pressure with a smaller elevation in gastric pressure. The over-all rise-time of the pressure change was 80–100 ms, similar to that for twitches produced by maximal phrenic nerve stimuli (Bellemare & Bigland-Ritchie, 1984; McKenzie & Gandevia, 1985). The diaphragm was not the only inspiratory muscle excited by the cortical stimulus. In two subjects needle electrode recordings from the fourth parasternal intercostal muscle revealed a short-latency activation at about 11 ms.

The scalp location at which cortical stimulation produced the largest response in the diaphragm was at or close to the vertex. Fig. 2 shows that both the e.m.g. response in the diaphragm and the twitch change in transdiaphragmatic pressure were larger with anodal stimulation at the vertex as compared with stimulation at more lateral sites (4–8 cm from the vertex). Similar results were seen whether the cathode was placed 6–7 cm anterior to the anode, or was distributed circumferentially around the head (Rossini *et al.* 1985). Stimulation laterally produces preferential activation of hand muscles whereas stimulation at the vertex activates the corticospinal projection to the lower limbs (Merton & Merton, 1980; Rossini *et al.* 1985). Because the best

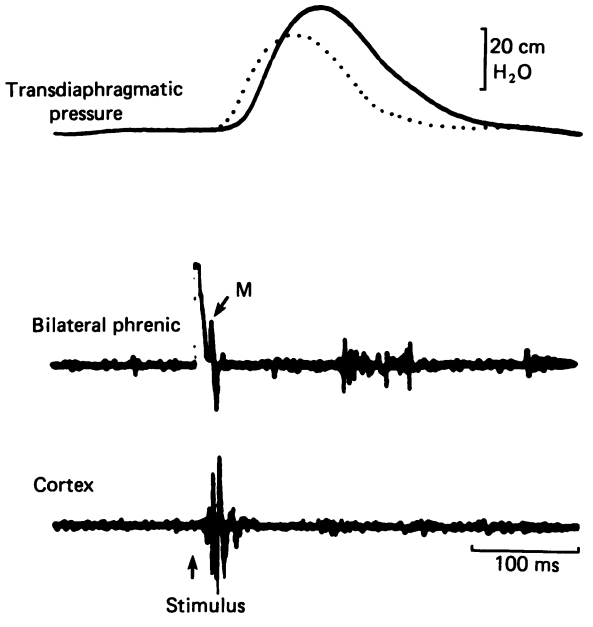

Fig. 1. Data from one subject showing transdiaphragmatic pressure and e.m.g. responses following cortical stimulation and bilateral stimulation of the phrenic nerves. The twitch pressure (transdiaphragmatic pressure) produced by cortical stimulation at the vertex (continuous line) is greater than that produced by a supramaximal stimulus to both phrenic nerves (dotted line). The e.m.g. responses were recorded with hook-wire electrodes inserted into the right costal diaphragm. The 'M wave' produced by the bilateral phrenic stimulus is marked. Two traces have been superimposed. Note the prolonged muscle action potential produced by the single cortical stimulus. Stimulus onset marked by arrow. Stimuli were delivered during a constant weak inspiratory effort at F.R.C. (with a transdiaphragmatic pressure of 10–15 cmH_2O). In this and subsequent Figures a negative potential at the 'active' electrode is shown as an upward deflexion.

scalp site for activation of inspiratory motoneurones was close to the mid line it was not possible to determine with certainty whether there was a bilateral projection to the phrenic motor nucleus. Activation of phrenic motoneurones from stimulation at lateral sites could have been explained simply by spread of the stimulus (up to 750 V) towards the mid line.

It was important to compare the estimate of central conduction time to the phrenic nucleus with that to other limb muscles because the latter projection is believed, on the basis of its short latency (about 4–6 ms; Marsden, Merton & Morton, 1983), to be oligosynaptic, possibly containing a monosynaptic component. In this study, estimates of 'central conduction time' to the diaphragm were compared with those to deltoid, made under identical conditions. Deltoid was chosen since its spinal motoneurone pool overlaps that of the diaphragm in the C5 segment of the cord. 'Central conduction time' was estimated by subtraction of the latency to stimulation of the spinal cord from the latency to stimulation of the motor cortex. A typical set of data from one subject is shown in Fig. 3 and the mean values for each subject shown in Table 1. In each subject the estimated central conduction time was similar for the diaphragm (range 4·0–4·6 ms; mean 4·3 ms) and the deltoid (range 4·0–4·8; mean

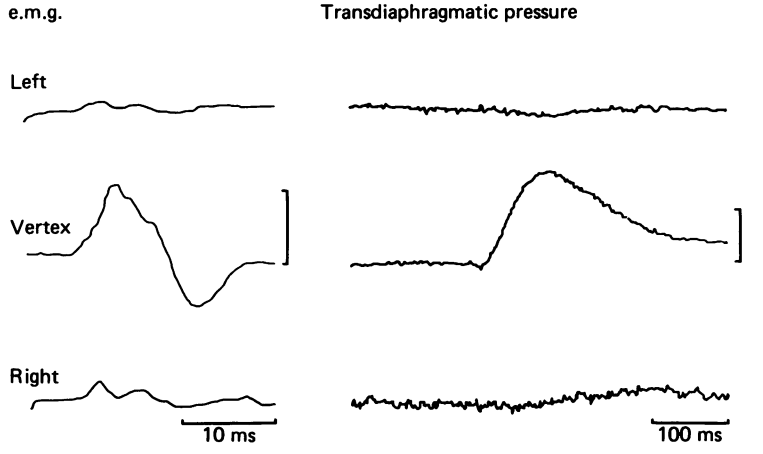

Fig. 2. Localization of the best point for cortical activation of the diaphragm in one subject. E.m.g. responses recorded via the gastro-oesophageal catheter are shown on the left and the mechanical responses (transdiaphragmatic pressure twitches) are shown on the right. All responses are the average of three to six trials. The maximal available cortical stimulus was used (see Methods). Bipolar anodal stimulation 7 cm to the left of the vertex (upper traces), at the vertex (middle traces) and 7 cm to the right of the vertex (lower traces). For each stimulus montage the cathode was located 7 cm anterior to the anode. The diaphragmatic response was larger for stimuli at the vertex than for stimuli on either side. All stimuli were delivered during a constant weak inspiratory effort (10–15 cmH_2O transdiaphragmatic pressure at F.R.C.). Vertical calibrations: left, 1 mV; right, 30 and 15 cmH_2O for vertex and lateral stimulation respectively.

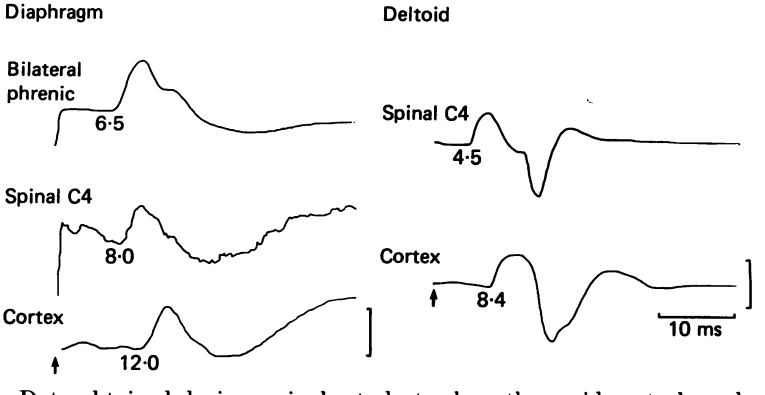

Fig. 3. Data obtained during a single study to show the rapid central conduction time from cortex to phrenic motoneurones (subject 1 in Table 1). E.m.g. responses for the diaphragm recorded via oesophageal electrodes (left) and for the anterior deltoid recorded via closely spaced surface electrodes (right). All stimuli on the left were delivered during a weak inspiratory effort at F.R.C. The difference between the latency for cortical and spinal stimulation is an estimate of the minimal central conduction time for the descending volley evoked by the cortical stimulus. Latency measurements are indicated in milliseconds. The central conduction time in the study was 4·0 ms for the diaphragm and 3·9 ms for the deltoid. Note the similarity in shape of the muscle action potentials to stimuli at the different sites. All responses are averages of four to ten stimuli. Cortical stimuli were delivered at the vertex and lateral to it for activation of the diaphragm and deltoid respectively (see Methods); spinal stimuli were delivered via a cathode at C4 (see Methods). Vertical calibrations: left, 1 mV; right, 1·5 mV.

TABLE 1. Latencies in milliseconds for the diaphragm and the deltoid to stimulation of the motor cortex and the spinal cord at C4 (see Methods). The latency to supramaximal stimulation of the right phrenic nerve is also shown. Measurements of diaphragmatic e.m.g. were made with the standard gastro-oesophageal catheter. Mean values from all experiments for a particular muscle are shown for each subject.

	Diaphragm				Deltoid		
Subject	Phrenic	Spinal	Cortex	Cortex–spinal difference	Spinal	Cortex	Cortex–spinal difference
1	6·6	8·2	12·2	4·0	4·6	8·6	4·0
2	5·7	6·8	11·4	4·6	5·2	9·5	4·3
3	7·5	9·1	13·4	4·3	5·2	10·0	4·8
Mean	6·6	8·0	12·3	4·3	5·0	9·4	4·4

4·4 ms). Particular attention was paid to ensure that spinal stimulation did not excite the motor axons distal to their exit from the spinal canal. This latter point was confirmed for the diaphragm by finding that the latency to stimulation of the phrenic nerves in the neck was 1·1–1·6 ms less than that to spinal stimulation. The latencies to the crural diaphragm from stimulation of the right phrenic nerve (Table 1) are well within the normal range established in this laboratory (McKenzie & Gandevia, 1985).

Single cortical stimuli activated the diaphragm preferentially when delivered during inspiration. The response to stimuli delivered during expiration was usually small or absent. However, Fig. 4 shows data from one study in which diaphragmatic responses during expiration (measured electromyographically or mechanically) were almost half the size of those during inspiration. The latency of the onset of diaphragmatic action potentials was 5 ms shorter for stimuli delivered during

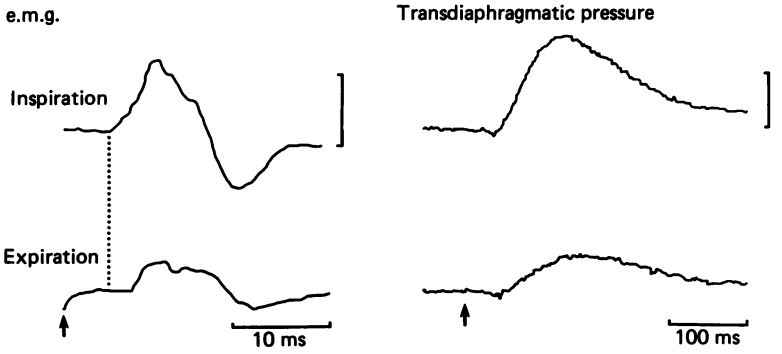

Fig. 4. Data obtained during inspiration (upper panels) and passive expiration (lower panels). E.m.g. responses (left) and mechanical responses (right) recorded via the gastro-oesophageal catheter. Cortical stimuli delivered at the vertex. Using a maximal cortical stimulus there was a larger response in the diaphragm for stimuli delivered during inspiration than expiration. In some studies the response for stimuli delivered during expiration was much smaller than that shown. Note that the latency of the muscle action potential to inspiratory stimuli was about 5 ms less than that to expiratory stimuli. All responses are averages of four to six stimuli. Vertical calibrations: left, 1 mV; right, 20 cmH_2O.

inspiration than expiration. This latency difference can be ascribed to the time required to raise individual motoneurones to firing threshold during expiration and/or to the decreased excitability of interposed interneurones during expiration. The latency to cortical activation of limb muscles may decrease by a similar amount when they are activated voluntarily (Day *et al.* 1986).

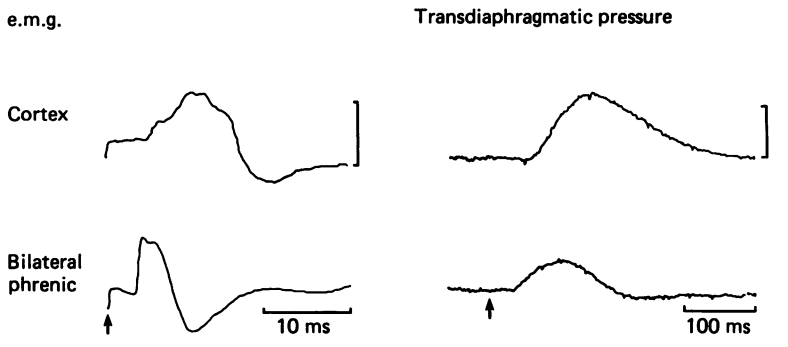

Fig. 5. Data obtained in one study to allow the comparison of the e.m.g. (left) and mechanical (right) responses to supramaximal stimulation of the phrenic nerves (below) with those to cortical stimulation at the vertex (above). Recordings made with the gastro-oesophageal catheter during a weak isovolumetric inspiratory effort at F.R.C. (averages of three to six traces). In this subject the muscle action potential produced by a single cortical stimulus was relatively long compared with that produced by a supramaximal stimulus to both phrenic nerves (cf. data from another subject in Fig. 3). A single cortical stimulus produced a mechanical response of greater amplitude and longer duration than that to maximal phrenic stimulation. Vertical calibrations: left, 1 mV; right, 25 cmH_2O.

It seemed that a single cortical stimulus may produce repetitive activity in diaphragmatic motoneurones. Evidence for this is obtained by comparison of the duration of the e.m.g. response to stimulation overlying the cortex and to bilateral stimulation of the phrenic nerves (Fig. 5, see also the intramuscular e.m.g. recording in Fig. 1). That this was not due solely to dispersion of the descending volley from the brain is suggested by the finding that the change in transdiaphragmatic pressure produced by cortical stimuli was much greater than that caused by phrenic nerve stimulation (Fig. 5).

DISCUSSION

Stimulation of the motor cortex through the scalp has revealed for the first time a comparatively direct projection from the motor cortex to the human diaphragm. This projection shares many of the properties which have been demonstrated for the corticospinal projection to limb muscles.

The present studies suggest that the estimates of 'central conduction time' from the motor cortex to the motor nucleus of deltoid or the diaphragm are the same (about 4·3 ms) in human subjects. This is consistent with the activation of a rapidly

conducting descending pathway to inspiratory muscles and to proximal muscles of the limb. It also fits well with the reported values of 5–7 ms for the central conduction time to distal muscles of the human hand which are innervated by lower cervical segments (Cowan, Dick, Day, Rothwell, Thompson & Marsden, 1984; Rossini *et al.* 1985; Snooks & Swash, 1985). While there may be some uncertainty as to which neural elements are excited by percutaneous stimulation of the motor cortex or spinal cord it should be stressed that the same techniques have been used to estimate central conduction delays for both diaphragm and the deltoid. We conclude that scalp stimulation activates both deltoid and phrenic spinal motor nuclei via rapidly conducting, mono- or oligosynaptic pathways from the motor cortex.

There is clear evidence in the monkey for a monosynaptic (corticomotoneuronal) pathway from motor cortex to motoneurones of the hand and forearm (Phillips & Porter, 1977). However, the existence of a corticomotoneuronal projection to the phrenic motor nucleus is still questioned. Data are available only for the cat. Colle & Massion (1958) reported activation at short latency of motoneurones innervating the median and phrenic nerves (on the contralateral side) after single stimuli to the motor cortex in the cat. Activation of respiratory motoneurones at short latency has been confirmed in other studies (e.g. Aminoff & Sears, 1971; Planche, 1972; Bassal & Bianchi, 1981; Lipski *et al.* 1986). In addition, there is anatomical evidence for a direct, possibly corticospinal, projection from the motor cortex to the region of the phrenic motor nucleus in the cat (Rickard-Bell, Bystrzycka & Nail, 1985). Recent electrophysiological studies have suggested that, at least in the cat, the short-latency excitatory response to cortical stimulation may be mediated by cortico-reticulo-spinal paths rather than corticospinal paths (Lipski *et al.* 1986). There is no evidence that this response is mediated via a synaptic relay involving medullary inspiratory neurones or brain-stem neurones involved in generation of the respiratory rhythm (Planche & Bianchi, 1972; Bassal *et al.* 1981; Lipski *et al.* 1986). While not formally investigated in the present study there was no overt 'resetting' of respiratory rhythm by the cortical stimuli. In conclusion, the present data would be consistent with the existence of a direct corticomotoneuronal or oligosynaptic cortico-reticulo-spinal pathway to human inspiratory motoneurones.

Single cortical stimuli can produce twitches in the distal muscles of the arm which are as large as those produced by supramaximal stimulation of peripheral nerve (Marsden *et al.* 1981; Rossini *et al.* 1985). Indeed, strong cortical stimuli often evoke contractions which are larger than those produced by peripheral nerve stimulation, indicating that the shock can give rise to repetitive firing of spinal motoneurones (Marsden *et al.* 1983). The same appears to be true of the projection to the diaphragm. The diaphragmatic twitch responses produced by cortical stimulation often exceeded those produced by supramaximal stimulation of the phrenic nerves (Figs. 1 and 5). However, this discrepancy cannot be explained simply by the activation of other synergistic inspiratory muscles (such as the parasternal intercostals) because of the marked prolongation of the diaphragmatic action potential evoked by single cortical stimuli (Figs. 1 and 5). This prolongation presumably reflects the ability of the cortical stimuli to evoke more than one descending volley along corticospinal paths (Landgren, Phillips & Porter, 1962; Day *et al.* 1986). Consistent with this is the observation that the latency of diaphragmatic activation was longer during expira-

tion than inspiration. A similar latency difference is seen in active and relaxed limb muscles (Day *et al.* 1986). It is thought that only during voluntary activation can the initial descending volley set up by the cortical stimulus activate motoneurones. In the absence of active facilitation, spinal motoneurones fail to discharge to the first descending volley and require summation of effects from later volleys. Irrespective of the specific mechanisms involved in the prolonged recruitment of phrenic motoneurones, the present results suggest that the projection to the diaphragm may be no less powerful than that to muscles of the upper limb.

Given these properties for the descending projection to phrenic motoneurones it is perhaps not surprising that, just as for limb muscles (e.g. Merton, 1954), the diaphragm can be completely activated during a maximal voluntary effort (Gandevia & McKenzie, 1985; see also Bellemare & Bigland-Ritchie, 1984). There are many non-respiratory motor tasks such as speech, which involve the respiratory muscles. However, it is unclear to what extent the rapidly conducting pathway to human inspiratory muscles documented here contributes to these tasks.

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