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How is ventilation maintained in the presence of the muscle relaxant, dantrolene sodium? A study in the anaesthetized rat

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1 The effects of intravenous injection of the muscle relaxant dantrolene sodium on ventilation, integrated EMG of external intercostal muscles and motor unit discharge in these muscles were measured in anaesthetized rats.

2 Dantrolene sodium was administered in a carrier solution at pH 10. The carrier was not responsible for the effects seen on dantrolene sodium infusion.

3 Dantrolene sodium (5 mg kg^{-1} body weight) reduced inspired ventilation ($\dot{V}_I$) on average from 308 ± 106 ml min^{-1} (s.d., $n = 8$) in the control period to 247 ± 118 ml min^{-1} ($n = 8$) after dantrolene sodium. Expired ventilation was reduced likewise from 274 ± 132 ml min^{-1} ($n = 8$) to 229 ± 109 ml min^{-1} ($n = 8$). These changes are significant at $P < 0.05$.

4 The integrated EMG was increased by 40.0 ± 29.3% ($n = 9$), a change significant at $P < 0.001$.

5 Dantrolene sodium not only decreased the mean interspike interval of individual motor units by 16.2 ± 11.1% ($n = 13$), a change significant at $P < 0.001$, but also increased the duration of the burst of activity of each individual motor unit on average by 36.2 ± 52.4% ($n = 13$), a change significant at $P < 0.05$.

6 The recruitment of additional motor units was also effected by dantrolene sodium. These units did not behave in any noticeably different manner from units previously active.

7 It is concluded that the nervous system compensates for the effect of dantrolene sodium only to a limited extent by increasing the frequency of discharge of active motor units. Recruitment of additional motor units and increased burst duration play at least as important a role.

Introduction

Dantrolene sodium is a muscle relaxant that acts directly upon the skeletal muscle fibres to uncouple excitation-contraction coupling (Ellis & Bryant, 1972). Intravenous injection of this drug reduces the amplitude of the skeletal muscle twitch by 70–75%. The finding, therefore, that the drug produces a minimal effect upon the respiratory variables of the anaesthetized cat (Bowman *et al.*, 1979) is somewhat unexpected. However, the action of the drug is highly dependent upon the frequency at which the muscle is stimulated (Bowman *et al.*, 1979; Leslie & Part, 1981). The maximum depression is produced at frequencies at which the motor units would be expected to be firing naturally. Bowman *et al.* (1979) have suggested that a reflex increase in the discharge frequency of the motor units enables the system to overcome the effects of the drug. This hypothesis remains untested; does the frequency of discharge of respiratory motor units increase and is the increase sufficiently great for it to be the sole factor in overcoming the effect of the drug? There are in addition other possible compensatory mechanisms; these include increased duration of discharge in each burst of activity, an increase of respiratory frequency and recruitment of motor units. The present experiments were designed therefore to determine the involvement of each of these possible mechanisms, both individually and collectively. The individual contributions were studied at the motor unit level, whereas their collective contribution was assessed from the integrated electromyogram (EMG) which gives the overview of the central nervous system's drive to the muscle.

A preliminary account of this work has been given to the Physiological Society (Farquhar *et al.*, 1985a).

Methods

The experiments were carried out on a total of 20 Sprague Dawley rats (female, 250–400g body weight). Anaesthesia was induced with trichlorethylene vapour and maintained by intraperitoneal injection of either urethane solution (1.5 mg urethane g^{-1} body weight) or Sagatal solution (5 mg $100g^{-1}$ body weight). Supplementary injections were given as necessary. No difference was noted between the results obtained when using either of the two anaesthetics. Deep body temperature was maintained between 36° and 38°C throughout the experiment by means of a heating coil placed beneath the animal.

The left femoral vein was cannulated for the injection of the drug, the carotid artery was cannulated for the measurement of arterial blood pressure and the right femoral artery was cannulated for the withdrawal of arterial blood samples. The trachea was connected via a cannula to a pneumotachograph (Mercury Electronics (Scotland) Ltd) the output of which was integrated by microcomputer (model 3D09, Digital, Design and Development, London). As both the positive and negative flow rates were integrated separately, values were obtained for both inspired and expired ventilation. The pneumotachograph system was calibrated by measuring, with a high sensitivity wet gas meter (Alexander Wright & Co. (Westminster) Ltd), volumes of gas passed at several constant flow rates, in known times.

Whole muscle electromyogram (EMG) recordings were obtained from a pair of surface electrodes placed on an external intercostal muscle on the right side. The amplified EMG was then rectified and integrated by means of a leaky integrator (Devices Ltd). The zero baseline for the integrated EMG was taken with both electrodes placed on inactive tissue. No calibration for this system was performed, the output being in arbitary units.

The single motor units were recorded by means of bipolar electrodes inserted into the external intercostal muscles on the left side opposite to the placement of the surface electrodes. The needle electrodes were made by pushing two strands of teflon coated silver wire (Medwire Corp.) down a 26 gauge hypodermic needle and holding the recording ends in place with Loctite Superbonder 495 (Loctite, U.K.). The single unit records were not only displayed and photographed conventionally from a cathode ray oscilloscope but were also analysed by the 3D09 microcomputer. The microcomputer ran the 6809 FLEX operating system. It was programmed in both BASIC and Assembler to analyse the discharge trains, burst by burst, in terms of the average duration of each burst and the average interspike interval within the bursts. (This software is freely available, on request to the authors.)

The experimental procedure involved first finding an active single motor unit with the needle electrode. The unit was further studied only if it could be distinguished from amongst recruited units. To test this, the respiration of the animal was stimulated by causing it to rebreathe its own expired air, a strong respiratory stimulation which causes the recruitment of additional motor units. Control readings were then taken of the discharge of the unit, the integrated EMG and the ventilation. In some experiments the carrier solution alone was investigated. In these experiments a 30 min recovery period was allowed before the administration of the dantrolene sodium. A period of 10 min of stable recording was required before administration of either carrier or drug. The use of a slow infusion apparatus allowed the administration of either drug or carrier to be undertaken at a constant rate over a period of about 10 min. Subsequent to these injections the recordings were continued for as long as the needle electrode system was able to discriminate the single unit.

The solution of dantrolene sodium was prepared immediately before injection as follows: 4 mg of hydrated compound were dissolved in 3 ml of NaOH solution at pH 10, whereupon 1 ml of 20% w/v mannitol solution was added; this isotonic solution contained 1 mg ml^{-1} of drug. The carrier solution referred to above was made in the same way but without the addition of the dantrolene sodium. In all experiments the drug was given at a final dosage of 5 mg kg^{-1} body weight, a dose known to have a

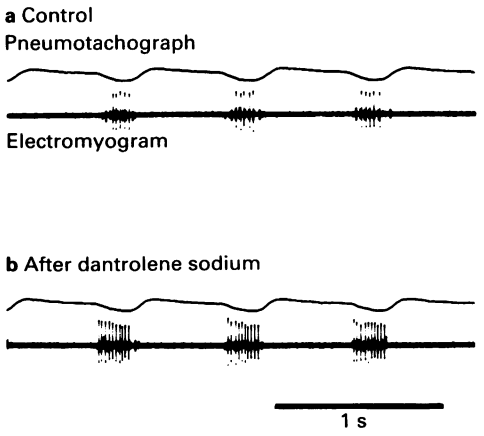

Figure 1 Simultaneous recording of a pneumotachograph tracing and electromyogram of a single external intercostal motor unit. Downward deflections of the pneumotachogram represent inspiration. Traces are shown before (a) and after (b) infusion of dantrolene sodium at 5 mg kg^{-1} body weight.

maximal effect on muscle twitch contraction (Leslie & Part, 1981).

Data handling and statistical analysis

Many of the results are presented as percentage normalised with respect to the control value equal to 100%. This method was used only after we had ascertained that the control data showed sufficiently small variation. Results are quoted as mean ± s.d., with the number of observations (n) in parentheses. Student's t test, paired or unpaired, was used to determine whether differences were significant; P values of 0.05 or less were taken as being statistically significant.

Drugs

The following drugs were used:- Trilene (trichlorethylene, Ph. Eur. I.C.I.), urethane (ethyl carbamate, B.D.H.), Sagatal (sodium pentobarbitone, May and Baker) and dantrolene sodium (a gift from Norwich Eaton Ltd, U.K.).

Results

It is known (Ellis *et al.*, 1976; Bowman *et al.*, 1979) that there is little or no change in an individual's or animal's ventilation during and after challenge with the muscle relaxant dantrolene sodium. Compensatory mechanisms must therefore be at work. These may include, among many possible mechanisms, the following four:- (i) an increase in frequency of discharge of the individual motor units, (ii) increasing duration of the bursts of activity, (iii) recruitment of additional motor units and (iv) change in respiratory frequency.

Our experiments were done therefore to determine how these four, acting individually and in concert, might contribute to the compensatory response.

Observations from individual motor unit studies

Figure 1 shows electromyographic recordings from a single motor unit before and after challenge with dantrolene sodium. After the drug there is a clear increase in the frequencies of discharge within each inspiratory burst of activity. This supports the hypothesis proposed by Bowman *et al.* (1979). Equally clear in this experiment (Figure 1) is the increase of burst duration, one of the other possibile mechanisms. In addition, the figure also shows that ventilation is little affected by the muscle relaxant; note the minimum of change in the pneumotachogram before and after the drug challenge.

Needle electrode recordings of single motor units, as typified by the EMG recordings shown in Figure 1, were presented to the computer for analysis. Measurements were made of both discharge frequency, expressed as mean interspike interval within the burst, and burst duration, taken as an average over some 20 inspirations. Such analyses from a single unit's discharge are shown graphically in Figure 2. It can be seen from this figure that during the infusion of the dantrolene sodium the interspike interval decreased; thereafter followed a period of variability before the interspike interval settled to a new lower value, that is the frequency of discharge had risen. For the motor units studied, the mean of the mean interspike interval post dantrolene sodium was some 16.2 ± 11.1% ($n = 13$) less than the mean of control data, a decrease significant at $P < 0.001$ by the paired t test. The unit illustrated in Figure 2 showed little increase in mean burst duration. In the sample population overall, dantrolene sodium caused a significant increase in the burst duration that averaged 36.2 ± 52.4% ($n = 13$), $P < 0.05$, by paired t test. Note however the large measure of variability; a reflection that while some units doubled their burst duration, others actually showed a slight decrease. In summary, dantrolene sodium causes both the interspike interval and the burst duration of individual motor units to be significantly altered. However, if the mean of the pooled control data is compared with the mean of the pooled post dantrolene sodium data, then overall there is found an insignificant change in both the samples' interspike interval and burst duration (see Figure 3).

This apparent paradox between the responses of individual units and of the total sample population

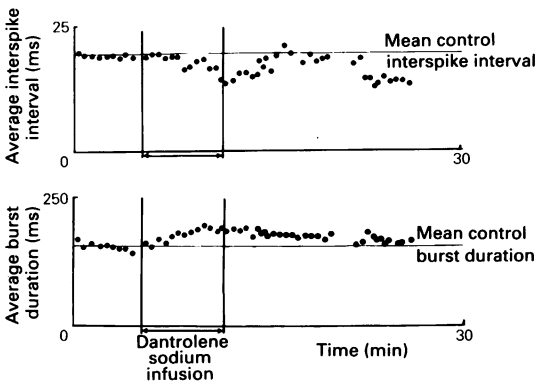

Figure 2 An example of a microcomputer print-out of the analysis of the discharge of a single external intercostal motor unit. In this experiment the dantrolene sodium (5 mg kg^{-1}) caused little change in the burst duration but after a period of fluctuation, an appreciable decrease in the interspike interval.

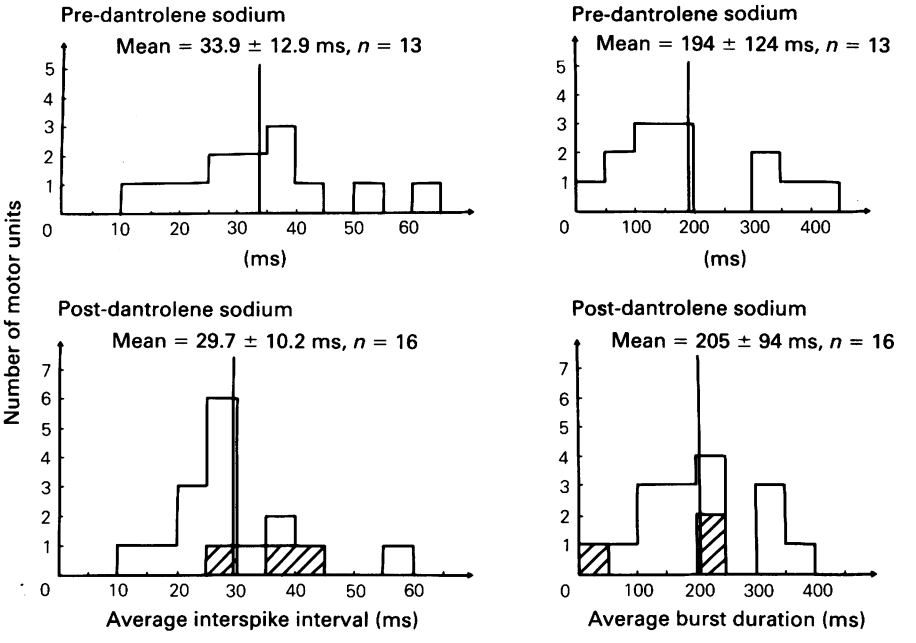

Figure 3 Histograms of motor unit interspike intervals and burst durations before and after dantrolene sodium (5 mg kg^{-1}). The means are indicated. The motor units recruited by the action of the drug are indicated by cross-hatching. Other recruited units could not be discriminated and so were not included in the histograms.

will be in part due to the variability of the magnitude of the changes shown by the individual motor units. Such variability was noticed in an experiment in which we were able to record the effect of dantrolene sodium on three motor units simultaneously; one unit showed an increase in discharge frequency with a small reduction in burst duration, the discharge frequency of another was unaffected but showed a slight increase in burst duration, and the third was only briefly recruited after injection of the drug.

Motor unit recruitment will also influence the integrated EMG. Such recruitment was often recorded in the background of our single unit recordings. The present experiments were not able to provide quantitative data on the overall extent of this recruitment. There are included however, in the post dantrolene sodium histograms (Figure 3), data from three recruited units. While these units provide an insufficient sample on which to make a full comparison between recruited units and those already active before injection of the muscle relaxant, it would appear that the frequencies and burst durations of recruited motor units were in no way exceptional.

Of the four mechanisms under consideration, the least affected by dantrolene sodium was respiratory frequency (see the lack of change in the periodicity of the pneumotachogram, Figure 1). Respiratory frequencies varied between animals and were no doubt in part dependent upon the level of anaesthesia. In the control period they ranged from 38 to 109 breaths min^{-1}, after infusion of dantrolene sodium the range was from 40 to 119 breaths min^{-1}. The mean change from before to after dantrolene sodium was only 6%.

The results from these single unit studies clearly indicate that, in the presence of dantrolene sodium, changes can and do occur in an individual motor unit's frequency and duration of discharge. Whereas these changes are in the main towards more and prolonged activity, the fact remains that some units in our sample showed little increase in frequency and/or a decrease in duration of their activity. Thus to determine the overall effect of these various changes and to assess the central nervous system's total drive to the whole muscle one must consider the integrated response.

Whole muscle integrated EMGs

Figure 4 shows collectively, from all experiments, the normalised changes brought about in both the rectified integrated EMG of external intercostals and inspired ventilation ($\dot{V}_I$) by either dantrolene sodium or alkaline carrier alone. The consistent finding was that dantrolene sodium caused an increase in the integrated EMG of external intercostals. Ventilation

Table 1 Effects of dantrolene sodium (5 mg kg^{-1}) and the alkaline carrier solution on the integrated EMG (arbitrary percentage units) and on the inspired and expired ventilation (ml min^{-1})

	EMG (%)	$\dot{V}_I$ (*ml min*$^{-1}$)	$\dot{V}_E$ (ml min^{-1})
Control	100	308 ± 106 (8)	274 ± 132 (8)
After dantrolene sodium	140.0 ± 29.3 (9)	247 ± 118 (8)	229 ± 109 (8)
Mean % change	+ 40.0 ± 29.3 (9)	− 17.1 ± 12.9 (8)	− 15 ± 16.4 (8)
Control	100	261 ± 95 (3)	259 ± 102 (3)
After carrier	82.2 ± 15.8 (4)	255 ± 98 (3)	249 ± 105 (3)
Mean % change	− 18 ± 16 (4)	− 2.4 ± 4.2 (3)	− 3.8 ± 9.3 (3)

The volume of carrier solution infused was the same volume that would have been used for dantrolene infusion to that animal. Results are given as mean ± s.d., number of readings in parentheses.

was, in contrast, either reduced or unaffected by the drug. The alkaline carrier on its own decreased the normalized integrated EMG; ventilation was little affected by the carrier. Statistics on these observations are presented in Table 1.

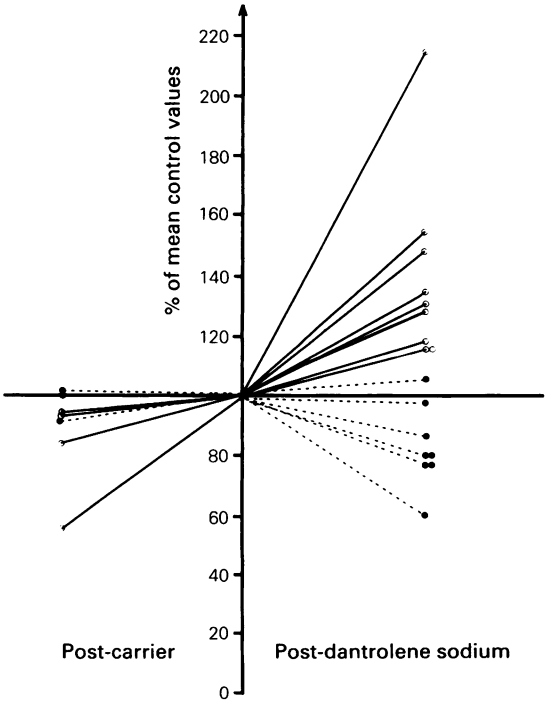

Figure 4 Changes in the percentage of mean control in the inspired ventilation (●) and the integrated EMG (○) by dantrolene sodium at 5 mg kg^{-1} body weight and by the alkaline carrier solution. The volume of carrier solution infused was the same volume that would have been used for a dantrolene sodium infusion to that animal.

The normalized integrated EMG was increased by dantrolene sodium on average by 40.0 ± 29.3% ($n = 9$), an increase shown by the paired t test to be statistically significant at the $P < 0.001$ level. Alkaline carrier infusion alone reduced the integrated EMG, on average, by 18 ± 16% ($n = 4$). Thus an important feature of Figure 4 is that the increase of integrated EMG evoked by the drug is, if anything, slightly under-estimated, since the carrier alone causes a reduction of the integrated EMG. Underestimate or not, these data clearly show that whatever the individual variations in a single motor unit's behaviour, the overall CNS response to dantrolene sodium is an increase of neural activity to the respiratory muscles.

On the other hand, ventilation ($\dot{V}_I$) was reduced by dantrolene sodium on average by 17.1 ± 12.9% ($n = 8$), a decrease significant at the $P < 0.05$ level. Expired ventilation (not illustrated in Figure 4) was also significantly reduced by 15 ± 16.4% ($n = 8$). Ventilation was little affected by the carrier. Whereas the infusion of a highly alkaline carrier might be expected to induce alkalosis and thereby a compensatory reduction in ventilation, the slow infusion rate (approx. 1 ml 10 min^{-1}) and buffering capacity of the blood were sufficient to maintain arterial blood pH within narrow limits. For example, in a typical experiment, the mean control pH was 7.375, the mean of three samples during a 10 min infusion of carrier alone was 7.352 and post-infusion the blood pH was 7.327. Changes in arterial pH due to carrier infusion do not appear therefore, in these experiments, to contribute to changes in ventilation. Thus a second important conclusion from Figure 4 is that the carrier solution contributes little to the reduction of ventilation seen in the presence of dantrolene sodium.

Though we have not investigated systematically the relationship between the integrated EMG and ventilation, the spontaneous variations that occur in any one recording period provide results over a range of values. Thus Figure 5 shows data from one experiment before and after dantrolene sodium. While statistically

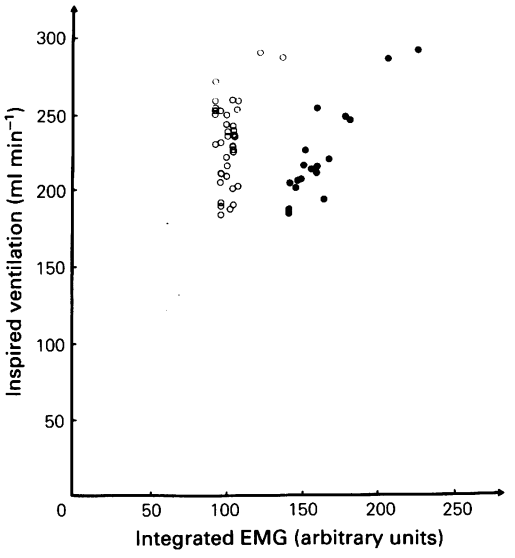

Figure 5 A graph of inspired ventilation plotted against the integrated EMG: (○) readings taken before the infusion of dantrolene sodium; (●) readings taken after the drug infusion. The readings were taken during spontaneous fluctuations of respiration.

there are poor but significant correlations between the variables, the data strongly suggest a drug-induced shift in the relationship, such that after administration of dantrolene sodium a given level of ventilation is associated with a greater integrated EMG from the external intercostals. Integrated rectified EMGs reflect the overall level of electrical activity in a muscle, and are related to its mechanical activity (Lippold, 1952; Bigland & Lippold, 1954). Thus it is probable that the external intercostals were making a greater contribution to ventilation after the drug challenge than before (see Discussion).

Discussion

Given the extent of muscle twitch relaxation produced by dantrolene sodium it is remarkable that an animal or patient receiving the drug suffers little (Ellis *et al.*, 1976) or no respiratory embarassment (Bowman *et al.*, 1979). For example these latter authors report that 'in 8 out of 12 experiments, dantrolene (at a dosage of 4 mg per kg) was without any detectable effect on breathing'. Our results from the anaethetized rat agree with Bowman *et al.* (1979) in that ventilation is sustained to a remarkable extent in the presence of the drug, albeit most rats showed some slight reduction in ventilation. For such maintenance of ventilation to occur, compensatory mechanisms, arising within the central nervous system, must be at work. Bowman *et al.* (1979), proposed a rapid reflex increase in the discharge frequency from the respiratory centre. The aim of our experiments was to investigate both this hypothesis and other mechanisms whereby ventilation might be maintained in the presence of dantrolene sodium. *A priori*, we might therefore expect increased electromyographic activity. Similar increases in EMG activity have been observed in the muscles of gait in the human following the oral administration of dantrolene sodium (Knutsson & Martensson, 1976).

As has been stressed before (Leslie & Part, 1981), the relaxant properties of the drug are dependent upon the stimulation frequency and contractile properties of the muscle. For example, while dantrolene sodium has a differential effect upon fast and slow contracting muscle, the effect of the drug on both types of muscle is limited at high stimulation frequencies, the relaxant effect at 200 Hz stimulation being only 18% and 12% reductions in tetanic tension of fast and slow muscle respectively. If therefore the motor control system were able to drive the motoneurones to discharge at these very high frequencies, as implicit in Bowman *et al.*'s (1979) hypothesis, then the effect of the drug would be almost completely overcome. Recording motor unit discharge frequency was therefore essential to gain an understanding of the manner in which the motor system is able to compensate for the muscle relaxation due to dantrolene sodium. The discharge frequency of individual motor units studied did increase significantly. But, the magnitude of frequency increase required for the unit to be spared the effect of the muscle relaxant depends upon the motor unit type, fast or slow (Leslie & Part, 1984). Fast motor units in the rat have their contractile tension reduced by 50% at about 150 Hz stimulation frequency whereas slow motor units have their tension reduced by 50% at about 30 Hz. In the present experiments there was no way of knowing the type of motor unit from which the single unit records were made. However, be the units slow or fast, their increases in discharge frequency were not sufficient for this effect to be the sole factor in the maintenance of ventilation in the face of the muscle relaxation. There was a significant increase in the discharge frequency of the individual motor units but if the frequencies of the overall populations are considered then it is apparent that the muscle has not been spared the action of the drug solely by means of an increase of discharge frequency. Other factors must be involved. One such is an increase in burst duration; this was observed to occur. An increase in burst duration will be effective in counteracting the action of the drug because repetitive stimulation in the presence of dantrolene sodium allows the build up of contraction albeit at a slower rate than without the drug (G.C.

Leslie and N.J. Part, unpublished).

Recruitment of additional motor units was also observed and must play an important role. It was not possible in the present experiments to obtain a quantitative assessment of the extent of motor unit recruitment. However it was apparent that the recruited motor units did not discharge in any markedly different manner from the units which were active before the administration of the drug. If all the motor units are active, recruitment is obviously impossible. These circumstances will normally apply in a maximum voluntary contraction. The effect of dantrolene sodium on the maximum voluntary contraction has been examined in multiple sclerosis patients (Mai & Pedersen, 1979). The drug reduced the maximum voluntary contraction in these patients by only 7% of the control value. In a maximum contraction it is probable that the great majority of the motor units are active and therefore it might be imagined that the only possibility available to the nervous system for overcoming the action of the drug is to increase the discharge frequency of the individual motor units. However, the subjects studied in the work of Mai & Pedersen (1979) had abnormal motor control and the value for the maximum voluntary contraction may have been reduced by activity in the antagonist muscles (Knutsson & Martensson, 1976). Dantrolene sodium will be equally effective on agonist and antagonist muscles and therefore, if this condition does apply, it might account for the relatively slight action of the drug on the maximum voluntary contraction of these subjects.

Control of respiration is complex, including reflex integration of proprioceptor and chemoreceptor inputs to the respiratory centre. The present experiments were not able to distinguish the relative contribution of each reflex component. We have however examined the action of dantrolene sodium on the tension and integrated EMG in the soleus of the decerebrate rat, in which a purely proprioceptive reflex may be studied (Farquhar *et al.*, 1985b). Our findings were not dissimilar to those presented here; frequencies of motor units already active were usually increased after challenge with the drug, and in addition there was motor unit recruitment. Changes in proprioceptive afferent inputs are therefore highly likely in the reflex maintenance of ventilation. The chemoreceptive reflex contribution to such maintenance of ventilation in the presence of dantrolene sodium has yet to be investigated.

Isometric contractile tension is proportional to the integrated EMG of a skeletal muscle (Lippold, 1952) as is the velocity of shortening (Bigland & Lippold, 1954). Our results (Figure 5) suggest a possible, slight, relationship between the inspired ventilation and the integrated EMG of the external intercostal muscles in the control period before giving dantrolene sodium. While the integrated EMG reflects the total activity in the external intercostal muscle, its activity need not necessarily be linearly related to the ventilation because in quiet resting respiration, the diaphragm will most particularly be playing a major role in inspiration. After challenge with the drug there would appear a stronger relationship between the external intercostal's integrated EMG and inspiratory ventilation. This may be interpreted as an increased involvement of the external intercostals in inspiration. Thus it would appear that not only are there compensatory mechanisms at work within a muscle, but also the central nervous system is calling into play a greater involvement of all inspiratory muscles to aid maintenance of ventilation.

When dantrolene sodium is used therapeutically it is of varying effectiveness despite acting directly on the muscle. These differences must reflect different responses by the central nervous systems of the different individuals. These results obtained from a respiratory muscle clearly indicate that three factors contribute to the neural compensation, namely (i) the increased frequency of discharge of the motor units, (ii) the period of time during which the motor units are active and (iii) the recruitment of motor units.

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