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The effect of dantrolene sodium on the discharge of alpha and gamma motoneurones to the soleus muscle in the decerebrate rat

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1 The effects of intravenous infusion of the direct acting muscle relaxant, dantrolene sodium (5 mg kg^{-1}), on tension, integrated EMG, soleus muscle motor unit discharge frequency and gamma nerve fibre discharge were measured in the decerebrate rat.

2 Dantrolene sodium did not have any detectable direct effect upon the discharge of the gamma nerve fibres.

3 The soleus muscle of the decerebrate preparations exhibited spontaneous tension and reflex responses.

4 With the muscle held at constant length, dantrolene sodium caused an increase in the integrated EMG in 15 out of 18 experiments and a decrease in muscle tension in 15 out of 17. The results from these experiments showed great variability.

5 Dantrolene sodium caused a slight reduction in the tension response to tonic stretch; this was accompanied by an increase in the integrated EMG.

6 Dantrolene sodium also caused a shift in the relationship between tension and integrated EMG during the phasic component of the stretch reflex, with a greater integrated EMG being associated with a reduced tension.

7 Motor unit discharge frequencies were found to increase but not sufficiently to overcome the action of dantrolene sodium. It is concluded that motor unit recruitment must play an important role in the compensation for the muscle weakening action of dantrolene sodium.

Introduction

Dantrolene sodium is a muscle relaxant which is thought to act by uncoupling excitation-contraction coupling (Ellis & Bryant, 1972) hence producing muscle weakness. Patients receiving the drug can maintain posture, respiration (Ellis *et al.*, 1976), maximum voluntary contraction (Mai & Pedersen, 1979) and movement (Knuttson & Martenssen, 1976). It has been suggested that this may be because of an increase in motor unit discharge frequency in response to the drug since the action of dantrolene sodium is highly dependent upon the frequency at which the muscle is stimulated (Bowman *et al.*, 1979), with the relaxant effect being much reduced at high stimulation frequencies.

It is possible that there may be a reflex response to the muscle weakness caused by the drug, for example a reflex increase of motor unit discharge frequency (Bowman *et al.*, 1979). We have investigated this point along with the other possible reflex responses such as recruitment of motor units and the results are presented in this paper.

In addition to its frequency-dependent effect on the contraction of extrafusal muscle, dantrolene sodium also has a frequency-dependent effect upon the contraction of intrafusal muscle (Leslie & Part, 1981). Because the gamma nerve system is able to bias the sensitivity of the stretch reflex, knowledge of the discharge pattern of the gamma neurones is required in order to understand the effect of dantrolene sodium on the system. This paper describes experiments in which spontaneous activity of gamma fibres was recorded before and after infusion of dantrolene sodium.

Although the drug consistently produces excitation-contraction uncoupling, its efficacy in treatment of spasticity is variable (Monster *et al.*, 1973). Therefore it is important to study the effect of dantrolene sodium on muscle tension in a reflexly active preparation. We

have previously described the mechanism by which the respiratory system is able to compensate for the muscle weakness produced by this drug (Farquhar *et al.*, 1986). The respiratory compensation for the effect of the dantrolene sodium depends to only a limited extent upon an increase in the discharge frequency of the motor units. The recruitment of additional motor units is at least as important. However, the reflex control of the respiratory muscles involves the chemoreceptors in addition to mechanoreceptors and proprioceptors. Therefore we have examined the effect of dantrolene sodium on the stretch reflex in the soleus muscle of the hind limb of the rat, measuring muscle tension, integrated whole muscle EMG and discharge frequency of single motor units.

The experiments were performed on the decerebrate rat. This preparation was used because it exhibits the stretch reflex, both phasic and tonic, and not because it was thought to provide a particularly good animal model for human spasticity (Landau, 1980). Nevertheless we consider that the results obtained from this preparation provide a useful insight into the manner in which the drug may be acting in pathological conditions.

Preliminary accounts of some of this work have been presented to the Physiological Society (Farquhar *et al.*, 1985; Farquhar & Part, 1986).

Methods

Reflex recordings

The experiments were carried out on 35 female rats, body weight 200–250 g. Following induction of anaesthesia with halothane vapour (4%) in O_2, anaesthesia was maintained with halothane at 1–2%. The femoral vein was cannulated for the later infusion of dantrolene sodium. In preparation for the decerebration, the carotid arteries were tied off so as to minimize bleeding during the procedure. Sufficient bone was removed from the skull over the cerebral cortex to enable all the brain rostral to the superior colliculi to be removed by aspiration. To protect the brainstem from damage during the removal of the forebrain, these regions were first isolated from each other by sectioning the brain with the suction needle at the superior collicular level. Anaesthesia was discontinued after completion of the decerebration. As the rats recovered from the anaesthesia, muscle tone developed, reflexes could be elicited and spontaneous movements were made by the animal. In order that these movements should cause the minimum of interference with electrical recording, the rat was placed in a perspex tube from which its limbs protruded. One hind limb was immobilized by encasing it in a plaster cast which was itself firmly clamped in position. The soleus muscle tendon was drawn through a previously made incision at the ankle and attached to a puller with the muscle length corresponding to that of joint mid-position.

Length changes were applied to the muscle by means of an electromagnetic puller (Pye Ling V100) supplied with waveforms generated by a Servomex (LF141) waveform generator. The puller system was fitted with a length feedback control system (Reinking & Stuart, 1974). The waveform generator was controlled by a Digitimer (4030). In some static stretch reflex experiments the muscle was attached to a micromanipulator rather than an electromagnetic puller.

The soleus muscle tension was recorded by means of a strain gauge tension transducer mounted between the puller and the muscle.

EMG recordings were made from the whole soleus muscle by means of teflon coated stainless steel wire electrodes introduced into the muscle in hypodermic needles and retained in place by a hook given to the ends of the electrodes. As the needles were withdrawn one electrode was left in position near the tendon and one at the belly of the muscle. With the electrodes so arranged it was possible to record the activity of the whole of this small muscle. It was not possible to keep in place needle electrodes for the recording of single motor units because of the spontaneous movements of the animal. However, it was possible to discriminate single units from some of the whole muscle recordings.

The whole muscle EMGs were rectified and integrated with a Devices 3520 EMG Integrator Conditioning Unit. This unit gives full wave rectification along with an RC smoothing circuit, the time constant of which could be switched between 200 ms, 500 ms and 2 s. The single motor unit recordings were analysed in terms of both their instantaneous discharge frequency and their average discharge frequency. Instantaneous discharge frequency records were obtained by use of a frequency meter (Neurolog 256 or 700). The dominant frequency at which the motor unit discharged could then be read by eye from the trace.

Gamma discharge recording

The rat was decerebrated and set up in the manner described above except that the hind limb was dissected so as to expose the soleus muscle and free the soleus nerve and in addition the femoral artery was cannulated for the sampling of arterial blood. The hind limb was then placed in a bath of paraffin oil over Tyrode solution as previously described (Andrew & Part, 1972). Spontaneous movements made nerve recording impossible and so the animals were paralysed with a dose of gallamine just sufficient to prevent spontaneous ventilation and then ventilated with a small animal ventilator (SRI 5056). To ensure

the correct level of ventilation, blood gas analysis was periodically performed on arterial blood samples; the arterial P_{CO_2} was kept within the range 35–45 mmHg.

The discharge was recorded from the proximal end of the cut soleus nerve. The nerve was desheathed for about 5 mm from the cut end before dissection into fine strands from which the action potentials of single nerve fibres could be recorded. A second pair of bipolar recording electrodes was placed on the sciatic nerve about 20 mm proximal to the section of the soleus nerve. With the spikes from the soleus nerve filaments as the trigger and the sciatic nerve recording as the input signal, the conduction velocity of individual nerve fibres was measured by the technique of spike-trigger averaging (Mendell & Henneman, 1968) using a Unimac (4000) hardwired laboratory averager. All of the spontaneously active fibres in this deafferented preparation had conduction velocities less than 32.2 m s^{-1} and therefore were gamma fibres (Andrew & Part, 1972; Andrew *et al.*, 1978). The discharge of the gamma fibres was analysed with a 3D09 microcomputer (Digital, Design and Development, London) using software running under the Flex operating system. The gamma discharge pattern was also displayed using a frequency integrator (Neurolog 600). The output of the integrator increases in a stepwise fashion in response to each trigger spike. The output therefore represents the number of spikes discharged. When the output is plotted against time using a pen recorder, the gradient of the line is proportional to the discharge frequency of the gamma fibre.

Statistical analysis

Student's *t* test, paired or unpaired (preceded by the F-test), was used to determine whether differences were significant; *P* values of 0.05 or less were taken as being statistically significant.

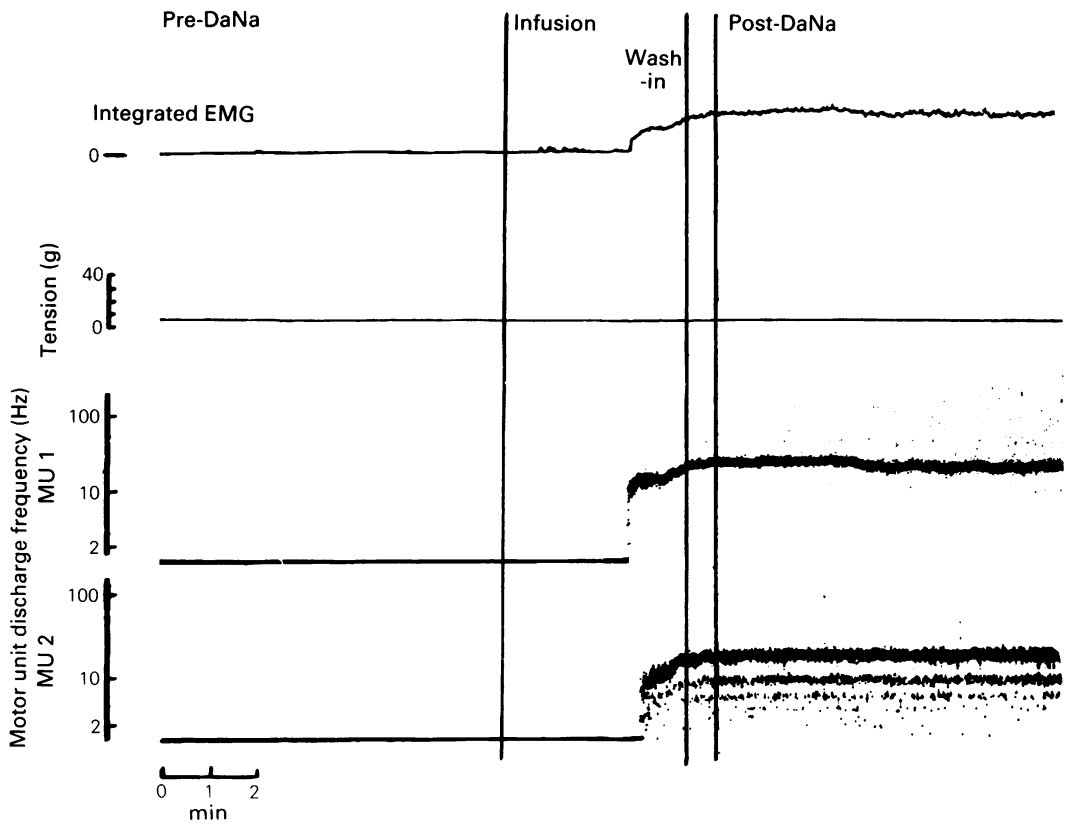

Figure 1 Traces showing the effect of dantrolene sodium (DaNa) infusion on the integrated EMG (top trace), total muscle tension and the discharge frequencies of two motor units in the soleus muscle of the decerebrate rat. When dantrolene sodium was infused, the tension remained unchanged but there was an increase of EMG activity.

Drugs

The following drugs were used: halothane (Fluothane, I.C.I.), dantrolene sodium (a gift from Norwich Eaton Ltd, U.K.) and gallamine triethiodide (Flaxedil, May & Baker).

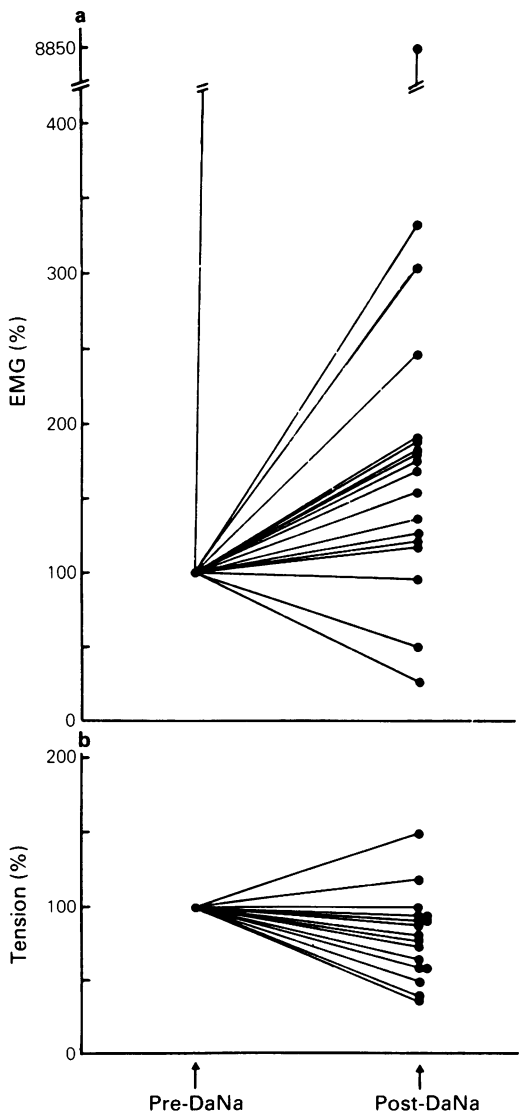

Figure 2 The effect of dantrolene sodium (DaNa) on integrated EMG in 18 experiments (a) and total muscle tension (b) in 17 experiments. The exceptionally large increase of integrated EMG in one experiment was excluded from the statistical analysis.

Results

Effect of dantrolene sodium on muscle at constant length

The soleus muscle of the decerebrate rat shows spontaneous EMG activity at the resting length. In most experiments infusion of dantrolene sodium caused an increase in electrical activity (Figure 1). In this experiment the tension remained unchanged when the drug was infused. It has been estimated that the rat soleus muscle has approximately 27–30 extrafusal motor units (Andrew & Part, 1972). In this experiment only two motor units were recruited in response to dantrolene sodium. There was little EMG activity or active tension before the drug infusion and hence the recruitment of just two motor units caused a very considerable increase in the EMG activity in percentage terms. Despite this large percentage increase of EMG it is apparent that there is no associated increase in tension, suggesting that, in the presence of the drug, greater EMG activity is required to produce a similar tension. The fact that the increase of EMG activity was

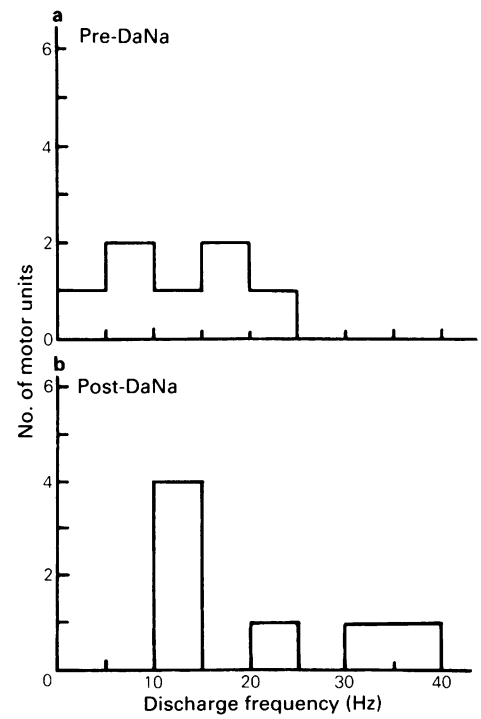

Figure 3 Histograms of the discharge frequencies of 7 motor units before (a) and after the infusion of dantrolene sodium (DaNa) (b). The discharge frequencies were read off the traces from the instantaneous frequency meter. The values obtained from each of the motor units were grouped, 0–4.9 Hz, 5.0–9.9 Hz, 10.0–14.9 Hz. . . .

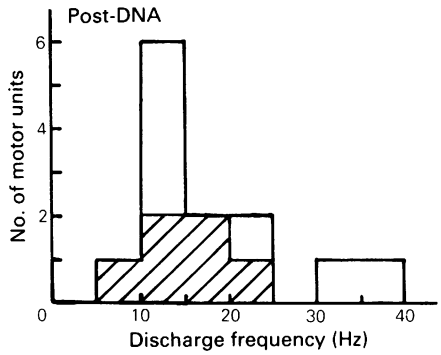

Figure 4 Histogram showing the discharge frequencies of all the motor units active after dantrolene sodium (DaNa) infusion. The values obtained from each of the motor units were grouped, 0–4.9 Hz, 5.0–9.9 Hz, 10.0–14.9 Hz . . . The units recruited as a result of the drug infusion are shown hatched.

exactly appropriate to maintain the original tension suggests it may have been a reflex response.

The responses to dantrolene sodium in all the experiments are summarised in Figure 2. In 15 experiments there was an increase in the EMG activity, in one experiment there was no change in the EMG and in two there was a decrease in the EMG. In two of the experiments there was an increase in tension on dantrolene sodium infusion but in all the others there was a decrease in tension. The paired t test showed that the increase in the integrated EMG ($P < 0.01$) and the decrease in tension ($P < 0.05$) were significant.

The discharge frequency of thirteen motor units from six muscles was recorded. Of these, seven were active before infusion of dantrolene sodium. The histograms of Figure 3 show the effect of the drug infusion on the discharge frequency of these seven motor units; none of the units recruited as a result of drug infusion are included in these results. The sample included both motor units with steady and varied discharge patterns. The frequency included in the histogram was the average frequency judged by eye

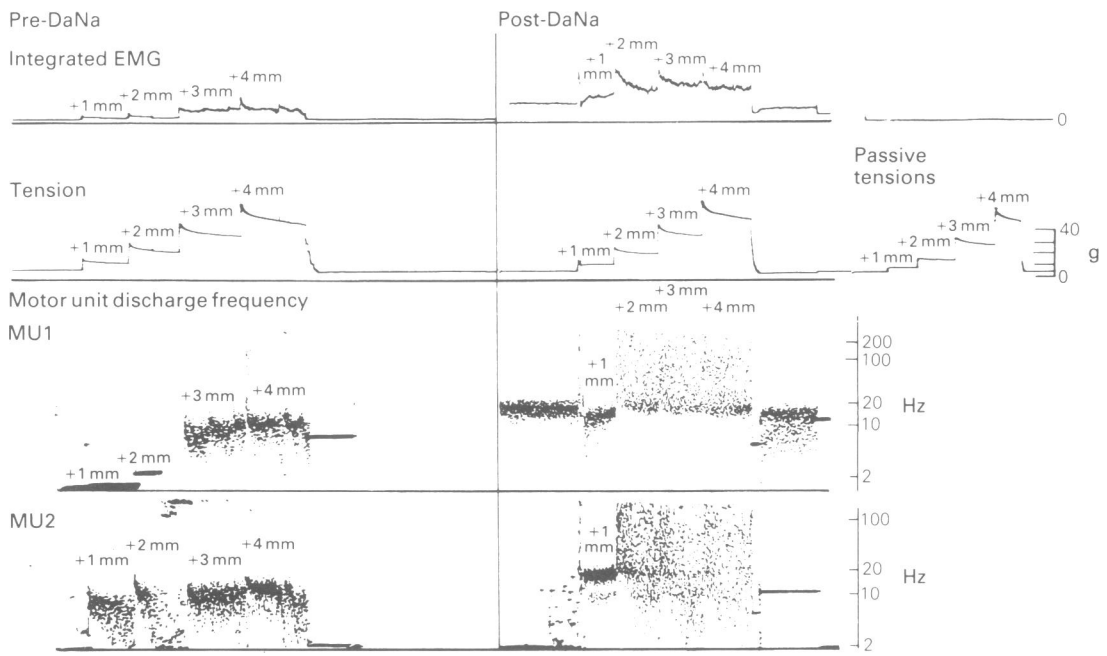

Figure 5 The traces, from the top, show integrated EMG, tension and the discharge frequencies of two motor units. The left hand records were taken before the infusion of dantrolene sodium (DaNa) and the right hand records after. Each trace shows the effects of stepwise 1 mm stretches of the muscle. When the muscle was held at an extended length, tension, integrated EMG and motor unit discharge frequency increased. The integrated EMG, tension and motor unit discharge frequencies at each muscle length in the presence of dantrolene sodium may be compared with the pre-dantrolene sodium values. At each muscle length, EMG activity was greater in the presence of the drug and the tension was reduced. The rate of stretch was not controlled in this experiment so there was sometimes a large dynamic response during stretch.

from the instantaneous frequency record. Six of the seven units had a higher discharge frequency in the presence of dantrolene sodium. The increase in discharge frequency of the units was found by the paired t test to be significant ($P < 0.01$) but the motor unit discharge frequencies reached were insufficient to spare the motor units from the relaxant action of the dantrolene sodium (see Discussion).

Recordings were made from 6 motor units that were recruited as a result of the infusion of dantrolene sodium. The discharge frequency of these units is represented on the histogram of Figure 4, along with those of the seven previously active units shown in Figure 3. It can be seen from this histogram that their discharge frequency did not differ from that of the units active before dantrolene sodium infusion.

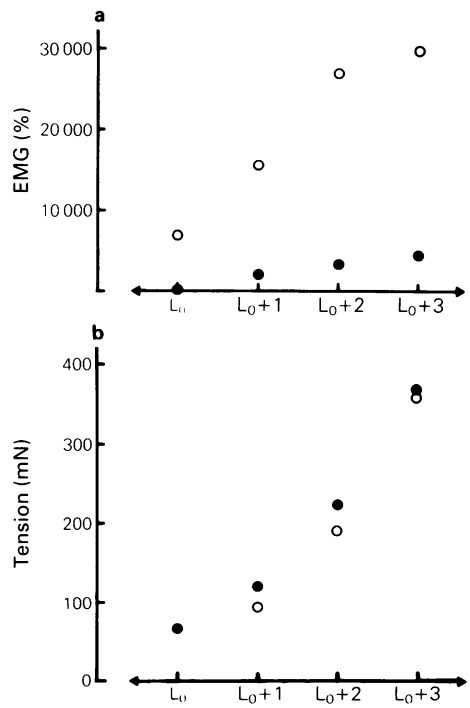

Figure 6 Graphs from an experiment illustrating the effect of dantrolene sodium on the response of the soleus muscle of the decerebrate rat to tonic stretch. The readings were all taken 30 s after the application of stretch: (a) integrated EMG plotted against muscle length before (●) and after the dantrolene sodium (○); (b) muscle tension against muscle length before and after the drug. Lengths are given in mm extensions from L_0, the length at the mid-joint position.

The effect of dantrolene sodium on the tonic component of the stretch reflex

The soleus muscle of the decerebrate rat shows a reflex increase in activity in response to sustained stretch similar to that originally described by Liddell & Sherrington (1924) in the decerebrate cat. Figure 5 shows an experiment demonstrating the effect of stretch on muscle tension and integrated EMG before and after the infusion of dantrolene sodium; also included in this figure are frequency displays of two motor units which could be discriminated from the EMG record. The results of an experiment are plotted out in Figure 6 in which it can be seen that as a result of the action of the drug the EMG activity has been substantially reduced at each muscle length and tension has been slightly reduced. The integrated EMG and muscle tension have been plotted against each other in Figure 7 in which it is apparent that the relationship between these two variables at each muscle length has been altered. The reduction of tension and increase of integrated EMG at each length was the usual finding with very few exceptions, although the shapes of plots varied. The results of similar experiments are presented in Figure 8.

The effect of dantrolene sodium on the phasic component of the stretch reflex

During phasic stretch of muscle in the decerebrate rat there is greater EMG activity and tension than during

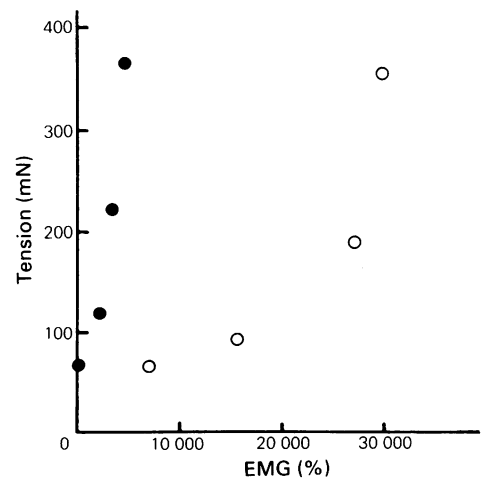

Figure 7 Graph of the results of the experiment of Figure 6 showing the shift in the relationship between the muscle tension and integrated EMG at each muscle length, caused by the infusion of dantrolene sodium: (●) represent results obtained before drug infusion, (○) results after dantrolene sodium.

the sustained stretch (see Figure 9). The relaxant properties of dantrolene sodium also affect muscle activity during phasic stretch. Measurements were made of the activity during the stretch by taking samples of the integrated EMG signal at four points during the stretch. These sample points were time locked to the stretch and so occurred at the same relative place in each trial and thus could be used to give comparisons of the responses to different stretches before and after the infusion of dantrolene sodium. The results of an experiment showing the effect of the infusion of dantrolene sodium are displayed in Figure 10. In five experiments there was an increase in the integrated EMG as a result of drug infusion. The paired t test reveals a significant difference between values of the integrated EMG at equivalent sampling points before and after infusion of dantrolene sodium. The effect upon the muscle tension was more variable; nevertheless it is clear from inspection of the pooled results (see Figure 11) from five experiments that the drug had shifted the relationship between the integrated EMG and tension.

The effect of dantrolene sodium on gamma nerve discharge

An appreciable amount of spontaneous nerve activity was recorded from the proximal stump of the desheathed soleus nerve in the decerebrate rat. Dissection of the stump permitted the recording from just a few nerve fibres at one time. Processing the resultant signal through a discriminator enabled the activity of a single nerve fibre to be analysed. The pre-trigger averaging techniques described in the methods section allowed conduction velocity measurement on single nerve fibres. None of the conduction velocities was greater than 32.2 m s^{-1} and hence all the spontaneously active fibres in this preparation are gamma as opposed to alpha (Andrew & Part, 1972; Andrew *et al.*, 1978). The dynamic gamma nerve fibres serving the rat soleus muscle tend to be the slowest conducting efferent nerve fibre to the muscle. The conduction velocity range of 9.3 to 32.2 m s^{-1} in the spontaneously active fibres in the decerebrate rat would suggest therefore that both static and dynamic gamma fibres are active in this preparation.

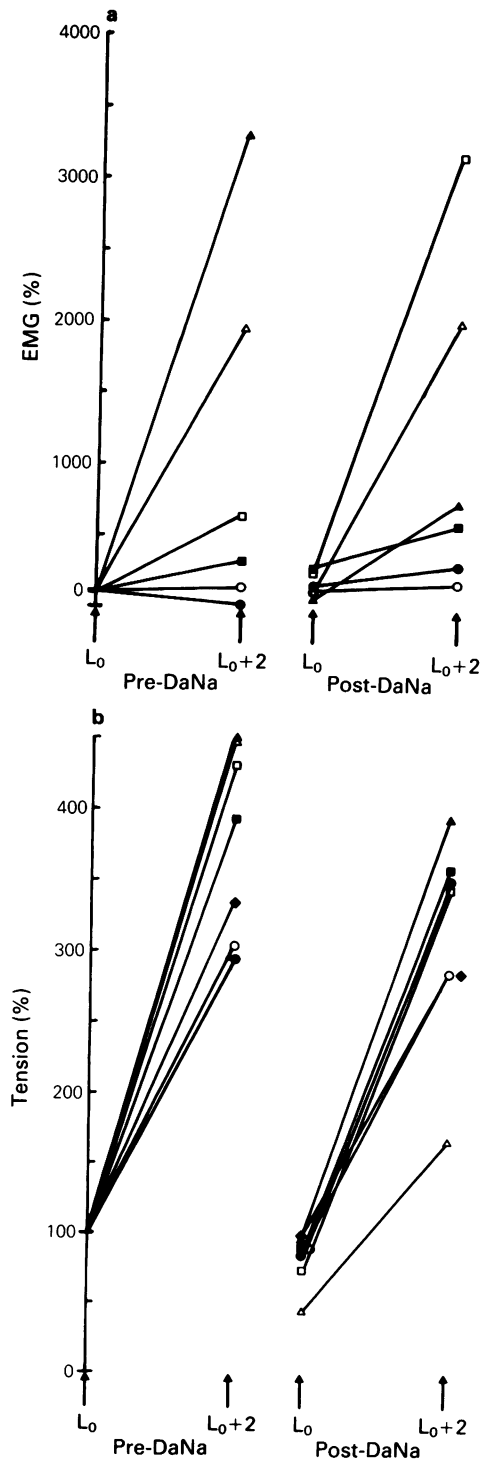

Figure 8 These graphs summarize the data obtained from experiments on the effect of dantrolene sodium (DaNa) on the tonic stretch reflex, 7 experiments for the tension and 6 for the integrated EMG. (a) Shows the change in integrated EMG produced by a 2 mm stretch both before and after drug. The data are normalized taking the integrated EMG at the resting length pre-dantrolene sodium as 100%. (b) Shows a similar plot for the tension data.

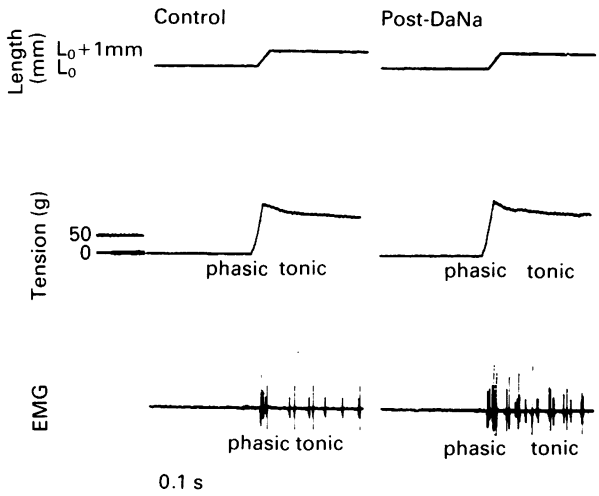

Figure 9 Experimental records showing the effect of dantrolene sodium (DaNa) on the phasic stretch in the soleus muscle of the decerebrate rat. The left hand column is, from the top, length, tension and EMG before drug and the right hand column shows similar records taken after infusion of the dantrolene sodium.

Following conduction velocity measurement, the discharge of the gamma fibre was analysed. Many of the fibres were not continuously active, firing instead in short bursts. Some otherwise continuously active fibres had short periods of inactivity and a few fibres had occasional periods of activity greater than the mean. The mean frequency of discharge for the continuously active fibres was measured with the frequency integrator. Examples of the records obtained are shown in Figure 12. The output of the integrator rises at each spike so that in the display, the number of spikes recorded is plotted against time and the gradient of each line is a measure of the gamma fibre discharge frequency. It is evident that the infusion of dantrolene sodium in this case does not bring about any detectable change in the discharge of the gamma nerve fibre. An analysis of the discharge of a gamma fibre discharging in the bursting manner is displayed in Figure 13 and it is apparent that the drug has not had any detectable effect upon the discharge. These experiments demonstrate that dantrolene sodium does not have any detectable direct action upon the gamma discharge to the acutely denervated soleus muscle of the decerebrate rat.

Discussion

These experiments have shown that the muscle relaxant drug dantrolene sodium has but a slight effect upon both the resting and reflex tensions of the decerebrate rat. The maintenance of tension despite the depressant action of the drug on muscle contractile tension involves an increase in the EMG activity of the muscle. Similar results have been obtained from the decerebrate cat (Harrison & Rawlinson, 1986). The increase in EMG activity is to some extent brought about by the observed increase in the discharge frequency of individual motor units. However, this frequency increase is by no means sufficient to account for all the increase in the integrated EMG and therefore recruitment of motor units must be playing an important role as in the response of the respiratory system to the challenge of dantrolene sodium (Farquhar *et al.*, 1986).

Whilst dantrolene sodium gave an increase in the activity of alpha motoneurones, we were not able to detect any change in the activity of gamma motoneurones. It should be noted however that the

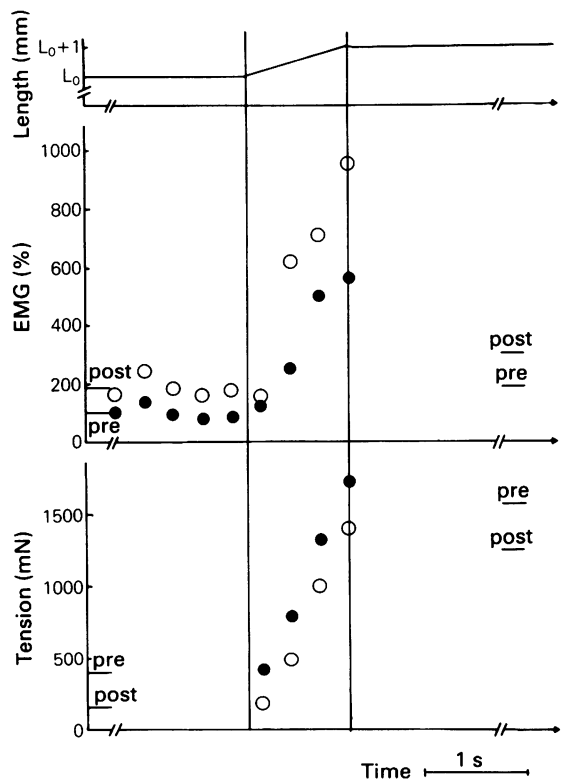

Figure 10 Top trace shows the stretch applied to the soleus muscle of a decerebrate rat. Plotted below are the integrated EMG (middle traces) and tension (bottom traces). These data refer to samples and hence are shown as points: (●) represent results before the infusion of dantrolene sodium and (○) results after dantrolene sodium. The mean integrated EMG and tension recorded while the muscle was held at L_0 and L_0 + 1 mm pre- and post-dantrolene sodium are indicated by horizontal lines.

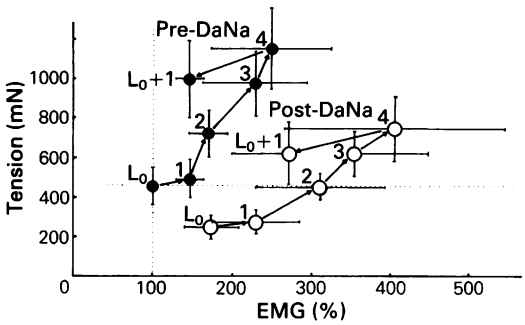

Figure 11 Shows data collected from 5 experiments of the type of Figure 10. The muscle tension is plotted against the integrated EMG at the resting muscle length and at the four sample points taken during the phasic stretch: (●) before the infusion of dantrolene sodium; (○) after infusion of dantrolene sodium. The bars refer to standard errors.

preparation used to investigate the effect on the two motoneurone types was not the same in that the gamma fibres were investigated in a preparation in which the soleus muscle nerve was cut and hence the receptor discharge from that muscle was not reaching the spinal cord. There was no alpha activity in this deafferented preparation which would suggest that the activity of these neurones is dependent upon an intact reflex loop. In contrast the gamma motoneurone discharge was maintained in our preparations without any muscle receptor input from the soleus muscle to the spinal cord. Data from the decerebrate cat strongly suggest that central drive to gamma motoneurones

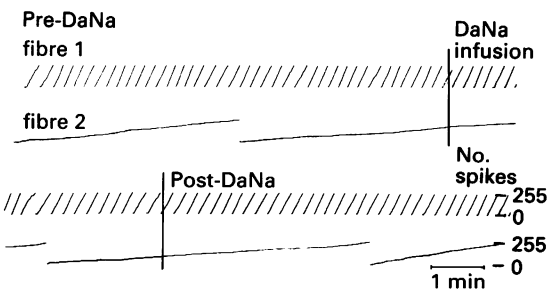

Figure 12 Integrated frequency displays of gamma fibre discharge. Each line shows the number of spikes discharged, 0–255, plotted against time so the gradient of each line is proportional to the discharge frequency of the gamma fibre. The records show the discharge of two gamma nerve fibres recorded simultaneously before, during and after the infusion of dantrolene sodium (DaNa).

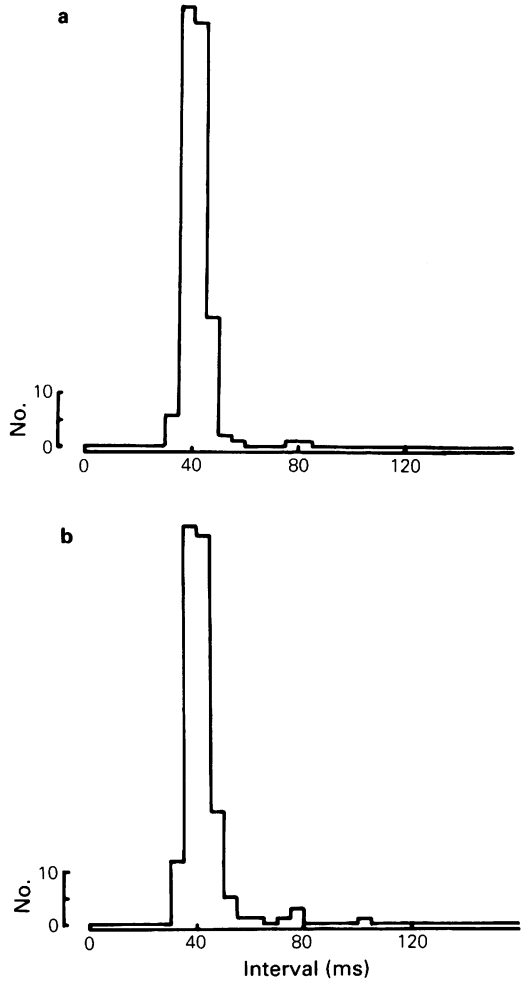

Figure 13 Histograms of the interspike intervals of a gamma nerve fibre with a bursting discharge pattern before (a) and after (b) the infusion of dantrolene sodium.

dominates the autogenic reflex effects such as the excitatory action of the muscle spindle primary (Ellaway & Trott, 1978). It is highly probably that, even in the reflexly intact decerebrate preparation, dantrolene sodium does not cause any change of gamma discharge frequency sufficient to put the discharge frequency into the range at which the drug has an appreciably reduced effect, that is approximately 100 Hz (Leslie & Part, 1981).

The alpha motoneurone discharge frequency was increased by infusion of dantrolene sodium. Comparison of the discharge frequencies recorded in this work with the previously examined frequency-related

reponse of the motor units to dantrolene sodium (Leslie & Part, 1984) shows that the increase was not sufficient, to spare the muscle from the action of the drug. As the tension of the muscle is so well maintained in the presence of dantrolene sodium, recruitment of additional motor units must play a very important role in minimising tension decrease. A similar conclusion was reached when considering how respiratory ventilation is maintained in the presence of dantrolene sodium (Farquhar *et al.*, 1986). However, in the action of the respiratory muscles there are also changes in the pattern of activity to be considered. The bursts of activity typical of the action of the inspiratory muscles are prolonged by dantrolene sodium. This is not a possibility with the continuous discharge of alpha motoneurones of the soleus muscle of the decerebrate rat and so recruitment is especially important in this case.

We have shown that dantrolene sodium does not have a direct effect upon the discharge of gamma nerve fibres in the decerebrate rat nor is there evidence that the drug has a direct action upon the discharge of alpha motoneurones. It is highly probable that the drug-induced changes in muscle activity are the result of spinal reflexes. This could only be fully established by experimenting with the dorsal roots sectioned.

There are a number of possible mechanisms by which the reflex control system could detect the muscle weakness induced by dantrolene sodium. Reduced extrafusal contraction would bring about reduced intrafusal muscle offloading and hence a greater excitatory input from the spindle afferents. The reduced extrafusal contraction would also reduce the golgi tendon organ input and hence the inhibitory effects of these receptors. However, the drug also acts upon the contraction of the intrafusal muscle and therefore the overall action of dantrolene sodium on the motor control systems must be complex. We have established in these experiments that the control systems are able to compensate remarkably well for the action of the drug.

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