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THE ACTION OF DANTROLENE SODIUM ON RAT FAST AND SLOW MUSCLE *in vivo*

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1 Rats, anaesthetized with urethane, were injected intravenously with dantrolene sodium in a carrier solution of 5% mannitol taken to pH 10 with NaOH. This carrier solution itself was without effect on extrafusal muscle contraction.

2 Dantrolene sodium (5 mg/kg) had a greater depressant action on the twitch contraction of the fast extensor digitorum longus (EDL) muscle than on the slow soleus (SOL) muscle. The EDL twitch was depressed to 25.9% ± 1.2% (mean + s.e. mean, $n = 7$) of control whereas the SOL twitch was depressed to 31.3% ± 0.4% ($n = 9$). These values are significantly different at the $P<0.001$ level.

3 The twitch contraction time to peak was reduced by approximately 35% in both EDL and SOL by dantrolene sodium. However, the drug reduced the half relaxation time of SOL by approximately 30% but that of EDL was hardly affected.

4 The effect of dantrolene sodium on contractions elicited by repetitive stimulation was dependent upon the stimulation frequency. For the SOL muscle the greatest depression was produced at a stimulation frequency of 25 Hz and for EDL at 75 Hz. The minimum of depression was produced for a full fused tetanus for both muscles.

5 The significance of these findings is discussed in terms of the action of dantrolene sodium on motor control in the intact animal.

Introduction

Bowman, Houston, Khan & Rodger (1979) have shown that in anaesthetized cats, the muscle relaxant drug dantrolene sodium (Dantrium, Eaton Laboratories, U.K.) has a greater depressant action on the twitch of fast muscle than on that of slow muscle. Kotsias & Muchnik (1978) in their study of the action of the drug on *in vitro* rat muscle did not observe any difference in the action of the drug on fast and slow muscle. We have investigated the action of dantrolene sodium on rat fast (extensor digitorum longus, EDL) and slow (soleus, SOL) muscle *in vivo*. Our results show that there is a difference in the action of the drug on the two rat muscles but that it is less pronounced than that shown by Bowman *et al.*, (1979) in the cat.

Methods

The experiments were carried out on nine rats (Sprague Dawley, females, 380 to 430 g). Surgical anaesthesia was induced with Trilene and maintained with an intraperitoneal injection of urethane (BDH, 30% w/v, 1.5 g/kg body weight). Deep body temperature was maintained between 35 and 37°C throughout the experiment by means of a heating coil placed beneath the animal.

The right jugular vein was cannulated for intravenous injection of the drug. Tension during contractions of the SOL and EDL of the left hind limb evoked by indirect stimulation was recorded as follows: preparation of the distal tendons for later attachment to the two force transducers; dissection of the muscles to free them maximally from all surrounding tissues but with great care taken to preserve the numerous blood supplies that can show, individually, substantial variations (Andrew & Part, 1972); the dissection of the soleus muscle nerve and also that of the common peroneal nerve distally, leaving intact only those branches innervating the EDL. When finally prepared, the leg was passed through a hole in the side wall of a perspex bath, which was then made leak-proof by raising, from the animal's thigh, a skin flap and tying it tightly to the flange surrounding the side entry (Close, 1967). The tibia was then securely clamped, as were the proximal tendon insertions of the EDL and SOL. The distal tendon of each muscle was cut from its insertion and directly attached to the cantilever beam of the force transducer. Thereafter the bath was filled with pre-warmed liquid paraffin floating on a layer of Tyrode solution and the contents maintained at 35 to 37°C by warm water circulating through a second chamber in the base of the bath.

Tensions developed by the two muscles were rec-

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orded with isometric force transducers (Devices Ltd, model 2ST02, 0 to 1 kg range) each having, in use, a compliance of less than 0.5 mm/kg load (and a natural resonant frequency at 1250 Hz). The amplified outputs from the force transducers were simultaneously displayed on a Devices two-channel pen-recorder and photographed from a dual beam oscilloscope (Tektronix 565). Whilst measurements of passive tensions were taken directly from the pen-recorder, most analyses of the various active tension records were made post-experimentally from projected enlargements of the film negative. Since the transducers were themselves mounted on separate micromanipulators it was possible to stretch each muscle independently. Initially the muscle was stretched until it was developing a measurable passive tension, only then was it stimulated indirectly, once every 5 (or 10) s. Thereafter the muscle was further stretched to that length, designated l_0 (Buller, Eccles & Eccles, 1960; Close, 1964), at which twitch tension was maximal. All data from these experiments were taken with the muscle rigidly held at its l_0 length. The muscle tension is expressed in the units of force per unit of muscle cross-sectional area. The force transducer was calibrated by hanging weights in multiples of grams from the cantilever beam and measuring the voltage output; grams were then corrected to mN by mutliplying by 9.81. The average cross-sectional area was estimated by dividing the mass of the muscle by the optimal length (l_0). Thus tension could finally be expressed as mN/mm^2.

The muscle preparations were stimulated indirectly through pairs of bright silver wire electrodes placed on the cut peripheral ends of the soleus muscle nerve and the common peroneal nerve (see above). Repetitive command programmes of stimulation were set up on Digitimers (4030) and used to control the timing of square wave output pulses from isolated stimulators (Devices Mk IV). Whole muscle twitch contractions were elicited once every 5 (or 10) s with supramaximal voltage pulses of 0.05 to 0.2 ms duration. Periods of tetanic contraction, evoked with frequencies of 10, 25, 50, 75, 100 and 200 Hz, lasted for 0.5 s. The programmes of stimulation were so arranged that (i) at no time were the two muscles contracting simultaneously, (ii) any post-tetanic changes of twitch tension resulting from one period of tetanic stimulation had reverted completely to control values before a second period of tetanic stimulation was applied and (iii) only twitch contractions were evoked in the 5 and 10 min periods before and after the intravenous injection of dantrolene sodium.

Our supply of dantrolene sodium was given to us by Eaton laboratories. The solution of dantrolene sodium for intravenous injection was freshly prepared for immediate use in each experiment as follows: 4 mg of hydrated compound were dissolved, by gentle heating and stirring, in 3 ml of distilled H_2O made alkaline to pH 10 by addition of NaOH; when fully dissolved a further 1 ml of 20% w/v mannitol was added and mixed thoroughly. This solution was given by slow intravenous injection at a dose of 5 mg dantrolene sodium/kg body weight and at a rate of about 1 ml per min. Control experiments were done with the carrier alone. After injection of carrier with or without the drug, the dead space volume of the polythene tubing to the venous cannula was flushed with normal saline.

Results

The effect of dantrolene sodium on twitch contractions of SOL and EDL

Injection of the NaOH-mannitol carrier solution (see Methods) was without any detectable action on the amplitude of the muscle twitch (see also, Leslie & Part, 1980). Figure 1 shows the effect of dantrolene sodium on twitch contractions of SOL and EDL. The results were obtained from oscilloscope and pen-recorder readings. The results obtained by these two methods differ quite considerably. The depression of twitch contraction produced by dantrolene sodium appears to be greater from the pen-recorder results and furthermore the relative difference between the effect on fast and slow muscle is exaggerated. The rate of contraction of rat muscle is such that not even a fast response pen-recorder such as the Devices M2 (3 dB down at 70 Hz) used in these experiments is sufficiently fast, accurately to capture the twitch contraction.

Therefore all the results considered in subsequent parts of this paper are taken from oscilloscope readings. The results from all successful experiments are included in Figure 1. The EDL twitch is more depressed with a mean final value of 25.9% ± 1.2% (mean ± s.e. mean, $n = 7$) of the control value as opposed to a final value for SOL of 31.3% ± 0.4% ($n = 9$). These values are significantly different at $P<0.001$.

Whilst the mean results from all the experiments show significant differences in the effect of dantrolene sodium on fast and slow muscle, this was not always the case with the results from individual experiments. In all experiments, however minimal the difference in effect of the drug, the EDL was always more affected than SOL.

In addition to reducing the amplitude of the twitch, dantrolene sodium reduced the time to peak (contraction time) of the twitch in our experiments on *in vivo* rat muscle (see Figure 2b). This is in contrast with the findings of Ellis & Bryant (1972) and of Bowman *et al.* (1979) who observed that in the cat the time to peak is unaltered by dantrolene sodium. It can also be seen in Figure 2a that the mean rate of rise of tension was also reduced by dantrolene sodium, for both muscles. In contrast the drug produced a differ-

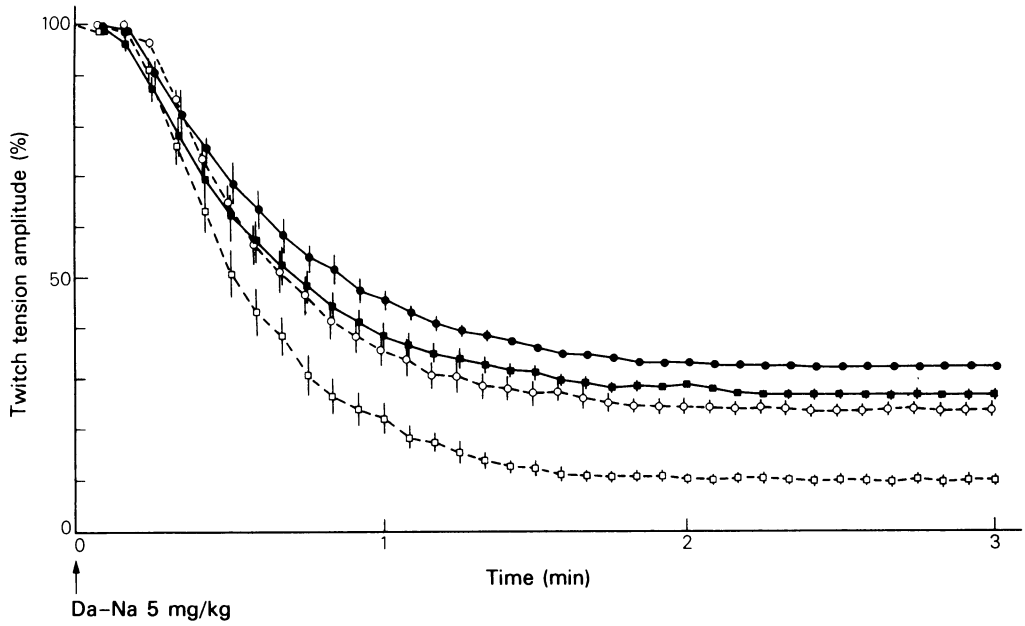

Figure 1 Illustrates the effect of a single intravenous injection of dantrolene sodium (Da-Na, 5 mg/kg) on the amplitude of twitch tensions developed by indirect stimulation of soleus (SOL, ●, ○) and extensor digitorum longus (EDL, ■, □) muscles, when measured from recordings taken simultaneously on a cathode ray oscilloscope (CRO, closed symbols, solid line) and pen-recorder (open symbols, dashed line). The amplitudes of the twitch tensions are, over the course of several minutes, greatly reduced from control values (≡ 100%), the fast EDL being more affected than the slow SOL. It is also clearly seen that markedly different quantitative impressions may be gained from the recordings made by CRO and by pen-recorder (see text for further comment). The data are presented as mean of n = 7 for EDL and n = 9 for SOL; vertical lines show s.e. mean.

ential response in the half relaxation times of twitches from EDL and SOL (Figure 2c).

The effect of dantrolene sodium on tetanic contractions

The muscles were stimulated for periods of 0.5 s at frequencies of 10, 25, 50, 75, 100 and 200 Hz and the maximum tension generated at each frequency was measured. Figure 3 shows the values of tension in EDL and SOL obtained from a single animal before and after the intravenous injection of dantrolene sodium. In both muscles the tension depression produced by the drug was dependent upon the frequency of stimulation. This is more clearly illustrated in Figure 4 in which the reduction of contractile tension produced by intravenous dantrolene sodium is shown plotted against the stimulation frequency. The depression of tetanic tension is greatest for EDL at a stimulating frequency of 75 Hz, whereas the depression of SOL tension is greatest at a stimulation frequency of 10 Hz. Data from all the experiments are shown collected together in Table 1. Considering these overall results, it is apparent that the results of the single experiment for EDL with maximum depression at 75 Hz are typical whereas the results for SOL with maximum depression at 10 Hz are not quite typical of the overall results in which the maximum depression is at 25 Hz.

In addition to the immediate effects of dantrolene sodium, Figure 3 shows the time course of the recovery from these effects. It is apparent that the relative recoveries of tension are dependent upon the stimulation frequency with the greatest recovery being shown at 100 Hz for EDL and 25 Hz for SOL (see also Figure 4).

Discussion

Our results on the effect of intravenous dantrolene sodium on the depression of twitch contraction of fast and slow muscles in the rat are qualitatively similar to

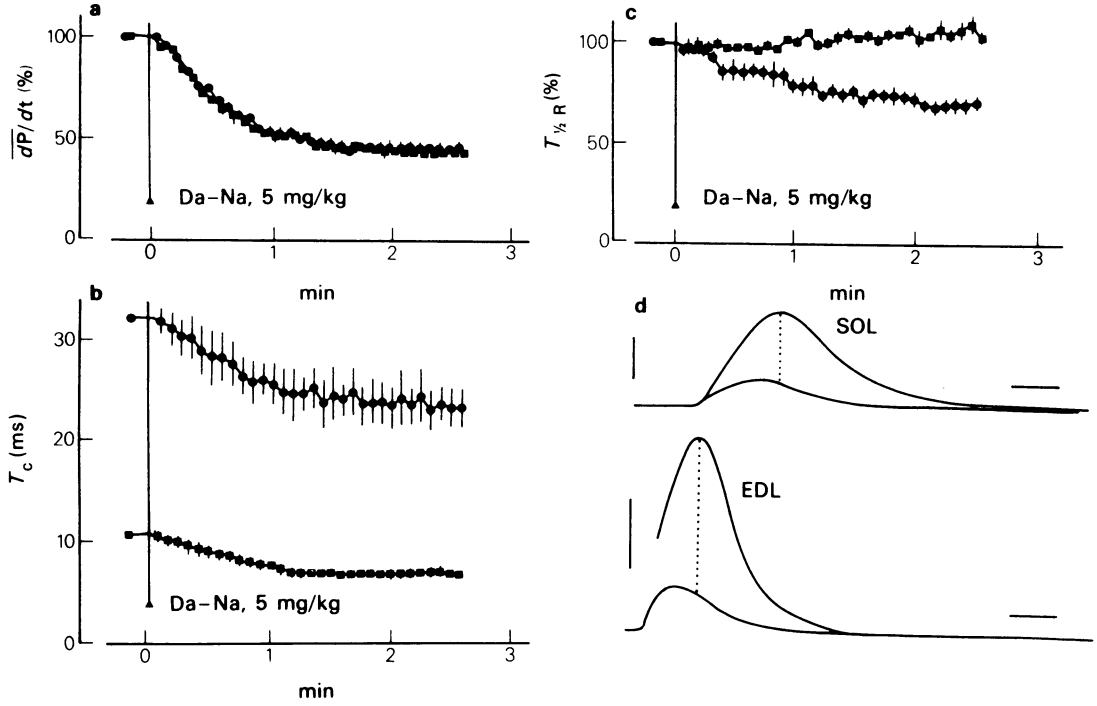

Figure 2 Shows the effect of a single intravenous injection of dantrolene sodium (5 mg/kg, given at arrow) on (a) the mean rate of rise of tension development (dP/dt); (b) the contraction time (T_c, as defined by Close, 1964); and (c) the half relaxation time ($T_{½R}$) of muscle twitches, as for examples in (d). The statistical data presented are mean n = 3 for both EDL (■) and SOL (●); vertical lines show s.e. mean. (a) Shows that dP/dt decreases by about 55% for both muscles; (b) shows that T_c for SOL falls from a mean value of 33.2 ms to 23.1 ms whilst that for EDL changes from 10.7 ms to 6.7 ms; in other words the percentage reductions in T_c are about 30% and 37% in slow and fast muscles respectively. (c) $T_{½R}$ for SOL is decreased significantly from control values (≡ 100%), $P<0.001$, whilst that for EDL remains little changed immediately after the injection of the drug. (d) Cathode ray oscillographic records of muscle twitches from SOL and EDL, before and after intravenous dantrolene sodium. The calibration bars to the left of the traces are normalized tensions equivalent to 25 mN/mm^2. The time calibrations are 10 and 20 ms for EDL and SOL respectively. The dotted vertical lines from the peaks of the control twitches have been inserted to emphasize particularly the reductions in contraction times.

those of Bowman *et al.* (1979) in the cat, in that the fast muscle undergoes a greater depression than does the slow muscle. However, our results differ quantitatively from those of these workers in that the differences between the fast and slow muscle are considerably less. Bowman *et al.* (1979) found the depression of twitch amplitude in cat flexor digitorum longus muscle (a fast muscle) to be about 90% as opposed to a depression of cat soleus twitch amplitude of 72%. These results from the cat indicate a highly significant difference in the magnitude of the action of the drug on fast and slow muscle in the cat. Dantrolene sodium in the rat, however, gives a depression of twitch contraction of 74.1% ± 1.2% (mean ± s.e. mean, n = 7) in EDL and 68.7% ± 0.4% (n = 9) in SOL, a smaller difference than that in the cat, but still significant at $P<0.001$.

The greater rate of contraction of rat as opposed to cat muscle makes it imperative that the oscilloscope be used for measurement of twitch amplitude rather than a pen-recorder, even of the fast response type. This point is illustrated in Figure 1 in which it can be seen that the pen-recorder results give a misleading impression of the relative action of dantrolene sodium on fast and slow muscle. Lack of frequency response of our pen-recorder system caused the differential action of dantrolene sodium on fast and slow muscle to appear exaggerated.

Our results from rat muscle differ from previously reported results from cat muscle not only in the lesser differential effect of dantrolene sodium on fast and slow muscles but also in the effect of dantrolene sodium on the time to peak of the muscle twitch. Ellis & Bryant (1972) and Bowman *et al.* (1979) found that dantrolene sodium had no effect on the time to peak in cat muscle; Figure 2b and d shows the reduction in

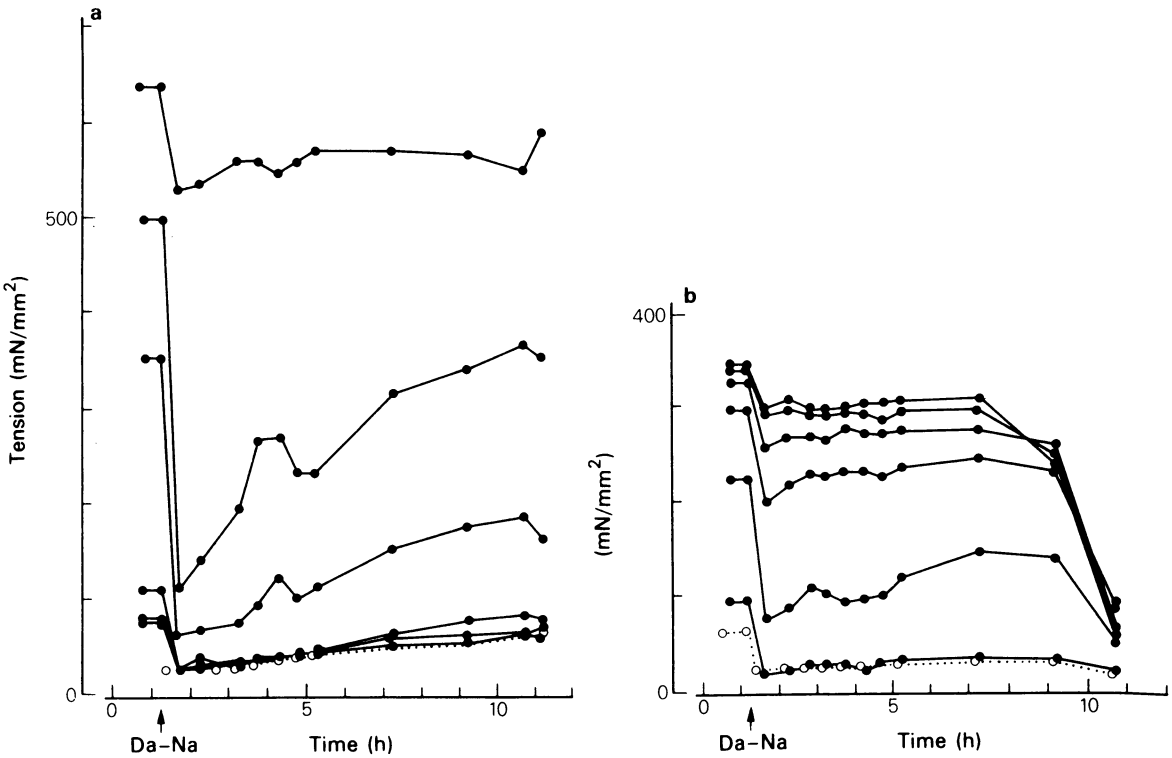

Figure 3 The immediate effect of a single intravenous injection of dantrolene sodium, and partial recoveries from same, on the maximum (normalized) tensions developed by EDL(a) and SOL(b) when stimulated at different frequencies (from top downwards: 200, 100, 75, 50, 25 and 10 Hz; the data shown by the open circles and dotted lines represent the tension developed in response to a single twitch stimulus given once every 10 s. The soleus preparation was clearly seen to fail some 7 to 8 h into the experiment; this was probably due to a failure of the blood supply to the muscle. Note that the EDL preparation was still viable at that time and was so for a further 3 h.

time to peak produced by dantrolene sodium in rat muscle. A similar reduction (about 35%) in time to peak has been observed from *in vitro* mouse EDL (Thapar & Ward, personal communication). Given both a reduction of twitch tension amplitude and a reduction of contraction time, it would not be impossible to have a set of those conditions when the mean rate of rise of tension was unchanged. However, in rat SOL and EDL the respective mean rates of rise of tension are reduced (see Figure 2a). This observation makes for agreement with Ellis & Bryant (1972), Nott & Bowman (1974) and Bowman *et al.* (1979) since all these authors' observations of reduced twitch tensions without change of contraction time must obviously have been associated with decreased values for mean rate of rise of twitch tension.

Our results confirm those of a number of authors (Ellis & Carpenter, 1972; Putney & Bianchi, 1974; Bowman *et al.*, 1979) that dantrolene sodium has a greater depressant action on the twitch contraction than on the fused tetanus. However, in the rat the greatest depression of contraction is produced at intermediate stimulation frequencies, 100 Hz for EDL and 25 Hz for SOL. These frequencies are those at which the contraction of the untreated muscle is just beginning to fuse. At these frequencies the changes in the time course of the contraction produced by dantrolene sodium are able to prevent fusion of the contraction and hence the great decrease in tension produced by dantrolene sodium at these frequencies. Bowman *et al.*, (1979) found similar results and came to similar conclusions. Mai & Pedersen (1979) have investigated the effect of intravenous dantrolene sodium on twitch and tetanic contraction of the soleus muscle of a multiple sclerosis patient. They found dantrolene sodium to reduce the twitch tension by 40% and the tetanic tension at 50 Hz by 5%, with no greater depression at any intermediate frequency.

Six hours after the intravenous injection of dantrolene sodium the contractile tension has recovered to some extent (Figures 3 and 4). Kotsias & Muchnik (1978) found that the twitch tension of rat muscle had returned almost to its control value 24 h after the intravenous injection of dantrolene sodium. The ex-

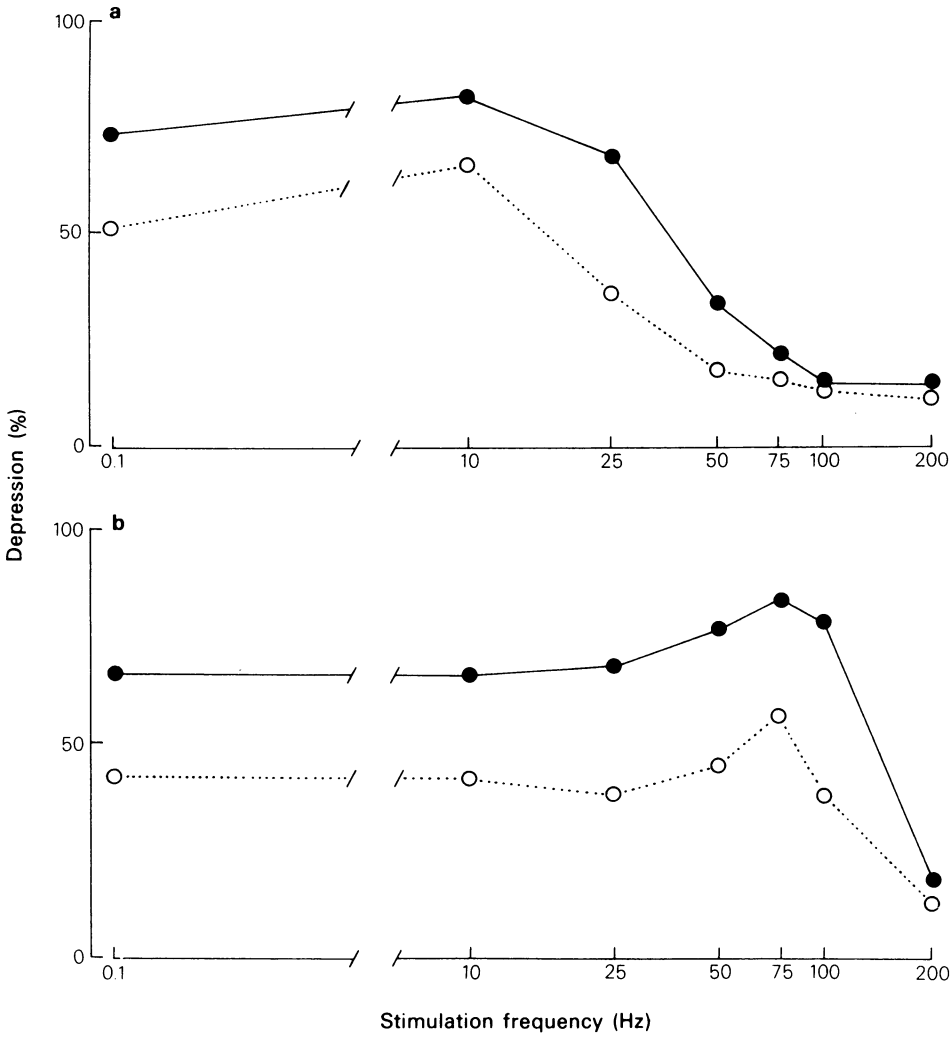

Figure 4 Percentage depression of contractile tension from control values (≡ 100%) plotted against the log of the stimulation frequency to SOL(a) and EDL(b). Results obtained immediately after an intravenous injection of dantrolene sodium (5 mg/kg) (●); values obtained 6 h after the time of the injection (○). The data presented in this figure were taken from the same single experiment illustrated in Figure 3.

Table 1 The statistical data (mean ± s.e. mean) for the percentage depression of contractile tension from control values (≡ 100%) against stimulation frequencies applied to the extensor digitorum longus (EDL) and the soleus muscle (SOL), immediately and at 6 h after a single intravenous injection of dantrolene sodium (Da–Na, 5 mg/kg), (See also Figure 4 and text)

Hz		*10*	*25*	*50*	*75*	*100*	*200*
EDL ($n = 6$)	Immed. after Da–Na	67.5 ± 1.3	71.3 ± 2.9	75.5 ± 1.4	84.0 ± 0.6	80.3 ± 1.2	18.3 ± 2.4
	plus 6 h	50.9 ± 4.8	54.0 ± 4.8	65.2 ± 4.5	73.2 ± 4.0	57.6 ± 9.8	16.8 ± 3.02
SOL ($n = 5$)	Immed. after Da–Na	64.4 ± 7.2	78.0 ± 3.3	40.9 ± 4.6	21.9 ± 4.09	20.6 ± 4.3	12.3 ± 2.7
	plus 6 h	54.9 ± 8.1	64.6 ± 7.4	26.4 ± 4.0	14.1 ± 2.7	13.7 ± 2.6	5.3 ± 2.8

tent of the recovery of tension is dependent upon the stimulation frequency, with the greatest recovery at those frequencies at which the greatest depression is shown. Presumably this can be explained from the effect of dantrolene sodium on twitch duration; as the effect of dantrolene sodium wears off, so the twitch will increase in duration causing increasing summation of contraction at these critical frequencies.

The action of dantrolene sodium in the intact conscious animal or human patient will depend upon a balance between the frequency of discharge at which the motor units are firing and their muscle fibre type, fast or slow. The slow postural muscles, such as soleus, have some motor units which show a continuous low frequency of discharge. In the decerebrate cat, soleus motor units discharge at 10 to 20 Hz (Denny-Brown, 1928; Granit, Phillips, Skoglund & Steg, 1957). Andrew & Part (1974) have recorded similar discharge frequencies in the slow motor units of the rat's tail. It is just at these frequencies that dantrolene sodium produces the greatest depression of the contraction of slow muscle. There is less information available as regards the discharge frequency of fast muscle but it would appear that the discharges occur in short bursts at a somewhat higher frequency than that of the slow muscle (Adrian & Bronk, 1928; Granit *et al.*, 1957). This means that again for fast muscle, the discharge frequencies are in the region at which the depression produced by dantrolene sodium is greatest. In fact, the depression of contractile tension is so great at the actual discharge frequencies of fast and slow muscle that, if under the action of dantrolene sodium the discharge frequency remained unaltered, the animal would lose the greater part of its muscle strength. Clearly this is not so, as the respiration of the anaesthetized cat is minimally modified by intravenous dantrolene sodium despite its depression of respiratory muscle contraction (Bowman *et al.*, 1979); these authors propose that a rapid reflex increase in the respiratory drive compensates for the depressed contractile tension. That some similar mechanism of compensation is operating for the limb musculature is suggested by the very small reduction (about 7%) in sustained voluntary power produced by intravenous dantrolene sodium in multiple sclerosis patients (Mai & Pedersen, 1979). In this case the relevant reflexes would be rather different in that the limb muscles do not have reflexes equivalent to those originating in the chemoreceptors but they are well served with reflexes originating in the muscle spindles and the Golgi tendon organs. Whatever the cause of the increased excitation of the motoneurones, it must be a potent one to enable them to fire at frequencies at which the depressant action of dantrolene sodium is slight; these frequencies being well above the naturally preferred discharge frequencies.

It would be expected that dantrolene sodium would be equally effective as a muscle relaxant for all cases of muscle spasm since it acts at the level of excitation-contraction coupling actually within the muscle (Morgan & Bryant, 1977). In fact dantrolene sodium is of different efficiency in the treatment of different muscle spasms and spasticity depending on their cause. In this context the complications introduced by any action of dantrolene sodium on the intrafusal muscle of the spindle is often considered. Opinions differ as to the effect of dantrolene sodium on the intrafusal muscle; Zorychta, Esplin, Capek & Lastowecka (1971) state that dantrolene sodium prevents the acceleration of spindle afferent discharge caused by gamma nerve fibre stimulation, whereas we have shown that dantrolene sodium merely reduces the effect of fusimotor stimulation (Leslie & Part, 1980). Dantrolene sodium also appears to differ somewhat in its relative effect on fast and slow muscle between different animals. In addition to these complications, the results in the present study show that the depression of contractile tension is dependent on stimulation frequency. In the intact

animal, one would not expect the discharge frequency to remain constant in the face of reduced contractile tension produced by dantrolene sodium because of the action of the reflex control mechanisms. This speculation requires experimental investigation. Furthermore it must be borne in mind that dantrolene sodium is administered to patients with a variety of disorders of these complicated control mechanisms. Perhaps therefore the variation in the efficiency of the drug is hardly surprising.

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