Aminophylline and fatigue of adductor pollicis in man

C. M. WILES, J. MOXHAM*, D. NEWHAM AND R. H. T. EDWARDS
Department of Human Metabolism, Faculty of Clinical Sciences, University College London, The Rayne Institute, University Street, London

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Summary

1. The effect of intravenous aminophylline on the contractility of adductor pollicis has been studied in three subjects both in the fresh state and following the induction of muscle fatigue.

2. Aminophylline had no influence on the frequency-force relationship and relaxation rate of adductor pollicis in the fresh state.

3. Fatigue resulted in a selective depression of the force response to low and moderate frequencies of stimulation and a slight effect on maximum force production 10 and 35 min afterwards.

4. Aminophylline given prior to, during and/or after fatigue did not influence this selective low-frequency fatigue at 10 or 35 min.

5. Aminophylline at the concentrations obtained has no significant effect on muscle contractility or fatiguability in man.

Introduction

Muscle fatigue characterized by selective reduction of force in response to low or moderate frequencies of excitation (<30 Hz at 37°C) with preservation of force at high frequencies (50–100 Hz) occurs in a variety of muscles, including adductor pollicis [1], sternomastoid [2] and diaphragm [3, 4] following prolonged high work loads. Methylxanthine derivatives potentiate twitch force in fresh muscle and may reverse such 'low-frequency' fatigue in vitro at concentrations in the millimolar range [5], which, in the case of theophylline, are too toxic for use in man. However, recent evidence has suggested that much lower theophylline concentrations are effective in altering the contractile properties of the diaphragm in man and can reverse fatigue [6]. The potential importance of this finding led us to test the effect of theophylline on fatigue in adductor pollicis, where force production and level of excitation can be measured more directly and precisely than in the diaphragm, particularly during tetanic stimulation.

Methods

Subjects

The subjects were three of the authors, two male and one female, aged 31–36 years. No subject had evidence of neuromuscular disease. The subjects were familiar with the techniques used and gave informed consent. Approval for the procedures used had been obtained from the Committee on the Ethics of Clinical Investigations at University College Hospital.

Techniques

Isometric force and muscle action potential amplitude were measured in left adductor pollicis in response to supramaximal stimulation of the ulnar nerve at the wrist using 50 μs square-wave pulses of 50–100 V; resting tension was adjusted to 50% of the force of a supramaximal twitch [7]. The hand and forearm were prewarmed in a water bath at 45°C for 15 min and subsequently during the experiment heating was maintained by an infrared lamp, skin temperature being controlled at 38–39°C, which yields an intra-
muscular temperature of approx. 35–37°C [8]. The frequency–force (F/F) response of the muscle was generated by stimulating the ulnar nerve at known frequencies for set times using a Devices Digitimer (D4030), viz. 1 Hz for 5 s, 8 Hz for 5 s, 10 Hz for 5 s; 12 Hz, 15 Hz, 18 Hz, 20 Hz, 22 Hz for 3 s; 25, 30, 40, 50, 80, 100 Hz for 2 s. Each series was performed in ascending order of frequency with 30 s between each test. During each tetanus the amplitude of the evoked muscle action potential was carefully observed on a Disa electromyograph (Type 14All) to check that responses were supramaximal, and from time to time the stimulus voltage was increased to check this. Measurements of relaxation rate were made from the differentiated force record during the 30 Hz tetanus [9].

Fatigue of adductor pollicis was induced by intermittent brief voluntary contractions (1 s on/1 s off, paced by an electronic metronome) to a target fixed at 66% of the previously determined maximum voluntary contraction force until the target could no longer be achieved. Particular care was taken to maintain extension of the interphalangeal joint of the thumb during this procedure. Fatigue normally occurred at 8–10 min and was checked objectively by stimulating the ulnar nerve at 50–100 Hz. The force × time performed by each subject in the three experimental protocols was kept constant, being that force × time achieved in the first experiment.

Aminophylline was administered by intravenous infusion into the right arm at a dose of 6 mg/kg in the first 30 min and subsequently at 0.9 mg as used by Aubier et al. [6]. Venous blood levels were taken from the test (left) arm after each F/F response.

Protocol

Three experiments were performed in each subject on separate days 2–3 weeks apart. The protocols for the experiments were as shown below:

Expts. 1 and 2 thus tested the effect of aminophylline on the F/F curve in fresh muscle and the ability of the drug to reduce the degree of 'low-frequency' fatigue, whilst expt. 3 tested the effect of the drug given immediately after the contractions to assess the impact on recovery from fatigue. Serum theophylline levels were determined by EMIT homogeneous enzyme immunoassay (Syva).

Results

A total of four control F/F curves were obtained in each subject (Fig. 1), although one of these (the second in expt. 2) was made 30 min after a preceding test. The curves were closely similar in each subject. After aminophylline infusion (protocol expt. 1), which gave plasma levels of 11.5, 15.7 and 16.8 mg/l in the three subjects respectively, there was no shift in the F/F response (Fig. 1a), nor in relaxation rate. The fatigue protocol produced substantial low-frequency fatigue in each subject as judged by F/F curves 10 and 35 min afterwards (Figs. 1a and 1b). Maximum force, by contrast, declined much less, being on average 89.0% (range 81.8–97.5%) of the initial value at the end of each protocol. Aminophylline had no discernible effect on the degree of reduction in force production at any frequency at either 10 or 35 min (Fig. 1). Relaxation rate was not significantly altered at the time when F/F measurements were made. In expt. 1, aminophylline levels in each subject were 13.2, 14.4, 15.2 mg/l at the point of fatigue and 11.5, 14.1, 14.5 mg/l 10 min post-fatigue. In expt. 3, aminophylline levels were 14-7, 14-7 and 14-3 mg/l and in both experiments these levels were sustained to the end at about 40 min.

Conclusion

Although these experiments have been performed in non-naive subjects, the indices of

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Adductor pollicis fatigue

![Graph](image)

FIG. 1. Effect of aminophylline on ‘low-frequency’ fatigue. (a) F/F curves in subject A: ●, mean ± SD for four control curves obtained in the three experiments; □, curve obtained in fresh muscle following infusion of aminophylline; ▲, curve 10 min following fatigue (control); △, 10 min following fatigue contractions, during and after which aminophylline was infused; ∇, 10 min following fatigue contractions, at the end of which aminophylline infusion was started. The broken line indicates the mean fatigue values (drawn by eye). (b) Force of 20 Hz tetanus as a percentage of maximum force before (C), 10 min and 35 min after fatigue in three subjects, A, B, and C: A, control series, no aminophylline; Δ, aminophylline infused before, during and after fatiguing contractions; ∇, aminophylline infused only after fatigue.

Muscle contractility and fatigue are defined by objective methods, i.e. supramaximal stimulation of the peripheral nerve. Marked low-frequency fatigue was produced as defined by a shift in the F/F curve to the right and the depression of the ratio (force at 20 Hz)/ (force at 100 Hz). It was confirmed that this depression of force production at low frequency was not accompanied by a reduction in muscle action potential amplitude [1]. As previously suggested [10], such fatigue is thus due to impairment of a mechanism distal to sarcolemmal excitation in the activation sequence or to an alteration in the compliance of the series elastic component of the muscle [11]. Methylxanthine derivatives may enhance twitch response and reverse low-frequency fatigue by an effect on calcium release by the sarcoplasmic reticulum, but this requires high concentrations [5, 12, 13]. We find no evidence of an effect of aminophylline on adductor pollicis in the fresh or fatigued state at the concentrations therapeutically acceptable in man. It remains possible that the diaphragm is more responsive to aminophylline than adductor pollicis, but in view of the considerable difficulties associated with supramaximal phrenic nerve stimulation at high frequency in man, this explanation cannot be assumed without further validation. In vitro the F/F curves, development of low-frequency fatigue and the response to high concentrations of theophylline are the same in limb muscle and diaphragm [5]. Aminophylline is therefore unlikely to exert its therapeutic effect in man by an effect on the contractility of respiratory muscle.

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References


