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The effect of aminophylline on function and intracellular pH of the rat diaphragm

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The effect of aminophylline on function and intracellular pH of the rat diaphragm. C.D. Shee, A.M. Wright, I.R. Cameron.

ABSTRACT: We studied the effect of aminophylline on twitch tension (TT) and intracellular pH (pHi) in isolated rat diaphragm strips that were fatigued, hypercapnic, or hypoxic. Superfused muscles were directly stimulated at 0.5 Hz. The pHi was measured from distribution volumes of dimethyl-oxazolidinedione. Fatigue was induced by intermittent tetanic stimulation. Hypercapnia and hypoxia were produced by altering superfusate carbon dioxide tension (Pco_2) or oxygen tension (Po_2). Aminophylline (1.0 mmol·l^{-1}) reversed the twitch decay seen during fatigue or hypercapnic acidosis, and caused partial recovery of twitch depression during hypoxia. Muscle fatigue was not due to an intracellular acidosis. Both hypercapnia and hypoxia lowered pHi. Aminophylline did not alter pHi in unstimulated muscles, but caused a significant fall in pHi in stimulated muscles that were fatigued or hypoxic. High dose aminophylline improved twitch tension in diaphragm strips that were fatigued, acidotic, or hypoxic. Twitch potentiation was not due to an intracellular alkalosis. Aminophylline lowered pHi in stimulated muscle, and thus, theoretically, could sometimes be harmful in the treatment of muscle fatigue.

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The recognition that respiratory muscle fatigue may be important in the genesis of respiratory failure [1] has led to interest in drugs that might increase inspiratory muscle strength or reverse fatigue. Aminophylline infusion has been reported as improving diaphragm contractility in man and dogs [2, 3], although not all workers have found this effect in man [4, 5]. *In vivo*, aminophylline has many systemic actions that might enhance muscle contractility [6], whereas *in vitro* one can study the direct effect of the drug on muscle. It is known that methyl-xanthine derivatives can potentiate the twitch in fresh and fatigued isolated skeletal muscle [7, 8], but the mechanism of action is uncertain.

The cause of muscle fatigue is not known, but a contributing factor may be reduced calcium release from the sarcoplasmic reticulum (SR) following muscle excitation. This would lower the calcium available for activating contractile filaments [9]. *In vitro*, xanthines can increase calcium release from the SR [10] and this might partly explain their twitch-potentiating effect. An intracellular alkalosis can also facilitate calcium release from the SR [11], and it would be of obvious interest to know if xanthines increase intracellular pH (pHi). There is little information on the effect of xanthines on pHi, but in one study 2.0 mmol·l^{-1} theophylline was found to cause a marked intracellular alkalosis in frog sartorius muscle [12]. Whether lower concentrations of theophylline alter mammalian muscle pHi is not known.

We have previously shown that hypercapnia and hypoxia reduce twitch tension and pHi in isolated superfused rat diaphragm strips [13]. As severe hypercapnia and hypoxia can occur with respiratory failure it is important to assess the efficacy of aminophylline under these conditions. It is not known if an intracellular acidosis attenuates the twitch-potentiating effect of aminophylline. We have examined the effect, *in vitro*, of 1.0 mmol·l^{-1} aminophylline on rat diaphragm fatigue and pHi. We have also assessed the action of aminophylline on hypercapnic and hypoxic diaphragm muscle, and have measured pHi following these interventions.

Methods

Diaphragms were removed from male Cummins-Sprague-Europe rats (200–350 g) under ether anaesthesia. A thin strip (15 mm × 1.5 mm) was dissected from the right hemidiaphragm, parallel to the radial line of the fibres. A portion of the central fibrous tendon and

of the distal intercostal insertion were included. The muscle strip was mounted horizontally in a superfusion trough between a fixed hook and an isometric tension transducer (UC2 Statham).

The superfusate contained (in mmol·l^{-1}); NaCl 118; KCl 4.5; $MgCl_2$ 1.0; $CaCl_2$ 1.5; NaH_2PO_4 0.4; $NaHCO_3$ 28; dextrose 6. Tubocurarine (20 mg·l^{-1}) was added to produce neuromuscular blockade. To enable measurement of extracellular space (ECS) and pHi the solution contained 100 μCi·l^{-1} chromium-51 attached to ethylenediamine tetra-acetate (^{51}Cr-EDTA) and 10 μCi·l^{-1} ^{14}C-5, 5-dimethyl-2,4-oxazolidinedione (^{14}C-DMO) (Radiochemical Centre, Amersham). Solutions were gassed in reservoirs and warmed to 36°C before flowing rapidly under gravity through the trough at a constant rate. There were two reservoirs, and superfusates could rapidly be switched *via* a 3-way tap at the trough inlet. The temperature, flow rate and osmolality of the solutions were the same. As the small muscle strips were rapidly superfused, the electrolyte composition of the fluid in the trough remained stable during different experiments.

Prior to stimulation, diaphragm strips equilibrated in the superfusion trough for 15 min in a solution bubbled with 95% O_2/5% CO_2. Muscles were then directly stimulated at 0.5 Hz in a transverse electrical field applied to the bath fluid through platinum electrodes placed in the wall of the trough. Stimulation was supramaximal (10 V) with a pulse width of 0.1 ms. Twitch tension (TT) was displayed on a Lectromed MX 212 chart recorder. Muscle length was adjusted to give maximum isometric TT.

pH and gas tension measurements

After an experiment, two superfusate samples were taken from the trough adjacent to the diaphragm strip. The pH, oxygen tension (Po_2) and carbon dioxide tension (Pco_2) were measured at 36°C using a Corning 165 analyser. The mean of readings from the two samples was used. The pH electrode was calibrated against bulk buffers, which were checked against buffer standards (Radiometer, Copenhagen). The gas electrodes were calibrated with mixtures previously analysed with the Lloyd-Haldane apparatus.

Measurement of pHi

Diaphragm ECS was measured from the distribution volume of ^{51}Cr-EDTA [14] and pHi from distribution volumes of ^{14}C-DMO [15]. In preliminary experiments it was found that isotopes equilibrated within 10 min, and that there was no change in ECS or pHi after that time. Muscle and superfusate samples were weighed and then dissolved in 1.0 ml Soluene (Packard Ltd). Three drops of glacial acetic acid and 10 ml scintillant were added. The scintillant contained 5 g·l^{-1} diphenyloxazole and 0.06 g·l^{-1} phenyloxazolyl in a 4:1 mixture of toluene and Instagel (Packard Ltd). Vials were cooled and counted in a liquid scintillation-spectrometer (Intertechnique, Model SL30). Quenching was negligible with the small muscle samples (8–12 mg). Cross-over of counts between the two channels was determined using dilute solutions of the isotopes. Background counts were constant and were subtracted. In earlier experiments the tissue water of 33 diaphragm strips was determined by drying muscles to constant weight. The mean tissue water was 77±1% (±SEM).

There were four groups of muscles:

(a) Control group (n=14). Muscles were stimulated at 0.5 Hz for 45 min in hyperoxic solutions bubbled with 95% O_2/5% CO_2 (pH 7.43, Po_2 540 mmHg, Pco_2 35 mmHg). TT was measured at 30 and 45 min.

(b) Fatigue group (n=21). In preliminary experiments it was found that intermittent tetanic stimulation resulted in force loss that was more marked at low than high frequencies of stimulation, a form of fatigue known as "low frequency fatigue" [9]. Muscles were stimulated at 0.5 Hz in hyperoxic solutions (95% O_2/5% CO_2) and were subjected every 4 min to tetanic stimulation at 100 Hz for 30 s. After 30 min, TT was measured and muscles were allowed to recover (tetanic stimulation discontinued) either in the absence of aminophylline (untreated group, n=15) or in the presence of 1.0 mmol·l^{-1} aminophylline (n=6). Stimulation continued at 0.5 Hz, and TT was remeasured after 15 min recovery. A solution sample was frozen and the free theophylline level was later assayed by high performance liquid chromatography.

(c) Hypercapnic group (n=9). Diaphragms were stimulated in solutions bubbled with 30% CO_2/70% O_2 (pH 6.77, Pco_2 210 mmHg, Po_2 410 mmHg). TT was measured at 30 min. Exposure continued for a further 15 min hypercapnia without aminophylline (n=4) or with 1.0 mmol·l^{-1} aminophylline (n=5).

(d) Hypoxic group (n=15). In vitro preparations require a high superfusate oxygen tension to maintain oxygenation in the core. "Hypoxia" (Po_2 140 mmHg) was produced by bubbling with 73% N_2/5% CO_2/22% O_2 (pH 7.43, Pco_2 35 mmHg). This level of hypoxia was chosen as it did not cause contracture and because substantial recovery in contractile function will occur following reoxygenation. Diaphragms were exposed to hypoxia for 30 min. Exposure continued for a further 15 min hypoxia without aminophylline (n=7) or with 1.0 mmol·l^{-1} aminophylline (n=8).

In separate experiments, pHi was measured in unstimulated diaphragm strips. Muscles were superfused with a hyperoxic solution (95% O2/5% CO_2); 8 without aminophylline and 7 in the presence of 1.0 mmol·l^{-1} aminophylline.

Results are expressed as mean±SE. The difference between group means, using logarithmic transformation where appropriate, was calculated using Student's unpaired t-test.

Results

In fresh muscles the mean±SEM time to peak twitch tension was 22±1 ms, the mean time to half relaxation of the twitch 22±1 ms, and the mean maximal tetanic force 12±1 $N \cdot cm^{-2}$. These values are similar to those found by METZGER *et al.* [16], although maximum active tension was somewhat lower in our preparations, probably reflecting damage to the edges of the diaphragm strip.

Fatigue

After 30 min stimulation at 0.5 Hz, TT in control muscles fell to 74±4% (mean±SEM) of the initial value. There was a greater reduction in TT in the fatigue group, to 22±2% ($p<0.001$) (fig.1). This force loss was seen predominantly at low stimulation frequencies, "low frequency fatigue". For example, at 30 min, the ratio of force at 20 Hz to that at 100 Hz was 0.35±0.02 in the control group, whereas in the fatigue group it was reduced to 0.22±0.02. In the control group there was a further gradual reduction in TT over the next 15 min, to 60±3% of the initial value.

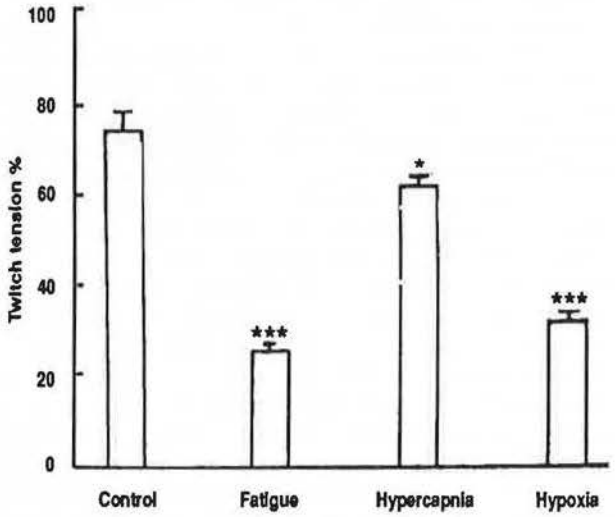


Fig. 1. – Mean (±SE) twitch tension (TT) values at 30 min in control diaphragms (n=14), and in diaphragms that were fatigued (n=21), hypercapnic (n=9) or hypoxic (n=15). TT is expressed as percentage of initial. *: $p<0.05$; ***: $p<0.001$ compared with control.

After 15 min recovery from fatigue, TT in untreated muscles rose to 108±3% of the 30 min value. With 1.0 $mmol \cdot l^{-1}$ aminophylline, TT increased to 251±17% of the 30 min value, and TT was actually slightly better than that of non-fatigued controls (fig. 2). The theophylline concentration in the superfusate was 370 $mg \cdot l^{-1}$.

At a superfusate pH of 7.43 the pHi of control, unfatigued muscles was 7.10±0.05. Intermittent tetanic stimulation (followed by 15 min recovery) resulted in a slight, but nonsignificant, reduction of pHi in the untreated fatigued group to 7.04±0.04 (fig. 2). The addition of aminophylline did not change superfusate pH but significantly reduced the pHi of fatigued muscles to 6.85±0.03 ($p<0.001$) (fig. 2). Aminophylline *per se* does not cause an intracellular acidosis as experiments on unstimulated diaphragm strips showed that pHi was similar in the absence of aminophylline (pHi 7.03±0.02) or the presence of 1.0 $mmol \cdot l^{-1}$ aminophylline (pHi 7.02±0.03).

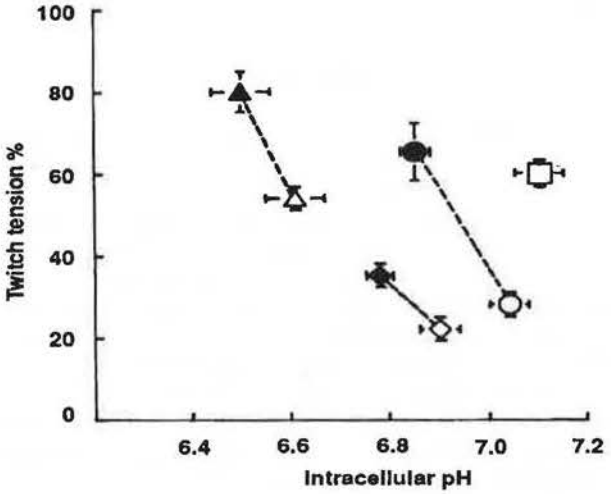


Fig. 2. – Mean (±SE) diaphragm twitch tension (TT) values at 45 min plotted against intracellular pH. TT is expressed as percentage of initial. Open symbols: untreated muscles; closed symbols: muscles treated with 1.0 $mmol \cdot l^{-1}$ aminophylline at 30 min; square: controls (n=14); circles: fatigued muscles (untreated =15; treated = 6); diamonds: hypoxic muscles (untreated =7; treated =8); triangles: hypercapnic muscles (untreated =4; treated =5).

Hypercapnia

After 30 min hypercapnia mean TT was reduced compared with that of normocapnic controls (fig. 1). In untreated muscles a further 15 min of hypercapnia produced a further fall in TT to 83±3% of the 30 min value. Despite continuing hypercapnia, there was actually a rise in TT in diaphragms treated with aminophylline, to 142±8% of 30 min value. In hypercapnic muscles treated with aminophylline, the mean TT at 45 min was higher than that of normocapnic controls ($p<0.001$) (fig. 2).

The pHi in untreated hypercapnic muscles was 6.61±0.06, which is significantly lower than that of 7.10 in normocapnic controls ($p<0.001$) (fig. 2). In hypercapnic diaphragms treated with aminophylline the pHi was 6.50±0.06 which is slightly but not significantly lower than in untreated hypercapnic muscles (fig. 2).

Hypoxia

After 30 min exposure to a superfusate of normal pH but reduced Po_2, TT was markedly depressed (fig. 1). In untreated muscles, TT continued to fall during a further 15 min hypoxia, to 69±6% of the 30 min value. Despite continuing hypoxia, there was a rise in TT in

diaphragms treated with aminophylline, to 111±2% of the 30 min value. The mean 45 min TT in aminophylline treated hypoxic muscles was still significantly lower than that of hyperoxic controls (fig. 2).

The pHi of hyperoxic controls was 7.10 and at the same superfusate pH 7.43, hypoxia reduced pHi in untreated muscles to 6.90±0.04 ($p<0.01$). In aminophylline-treated hypoxic muscles, pHi fell yet further to 6.78±0.03 ($p<0.05$).

Discussion

In control muscles, twitch tension (TT) decayed with time. This is seen in isolated muscle preparations containing a large number of type II fast fibres [17]. In diaphragms subjected to intermittent tetanic stimulation there was an initial short-lived reduction in tetanic force (high frequency fatigue). Following recovery of maximum tetanic force, there was a persistent reduction in TT, with development of low frequency fatigue. This type of fatigue is long-lasting and has been demonstrated in fatigued respiratory muscles [18]. It has previously been shown that 1.0 mmol·l^{-1} theophylline rapidly and completely reverses low frequency fatigue in isolated muscles [8], and we confirmed this with 1.0 mmol·l^{-1} aminophylline.

It is important to assess the efficacy of aminophylline in the presence of hypercapnic acidosis and hypoxia, because it is under these conditions that enhanced diaphragm contractility is most desirable. The pHi of muscle is readily altered by changes in P_{CO_2} [13, 14]. We wished to study the effect of aminophylline in the presence of a severe intracellular acidosis, and therefore the superfusate P_{CO_2} (210 mmHg) was made considerably higher than the arterial P_{CO_2} would be in respiratory failure. Even when hypercapnia lowered pHi to 6.61, aminophylline still remained effective, and TT actually increased to above that of control untreated preparations (fig. 2). Similarly, other workers have found that at non-toxic plasma levels the drug can reverse the depressant action of hypercapnia on canine diaphragm contractility [19].

"Hypoxia" was produced by decreasing superfusate P_{O_2} from 540 mmHg to 140 mmHg. This of course would not constitute hypoxia *in vivo*, but in isolated preparations a high superfusate P_{O_2} is necessary to ensure oxygenation in the muscle core [20]. Aminophylline improved TT during hypoxia, but values did not return to control (fig. 2), suggesting possible substrate depletion. Other authors have shown that aminophylline can improve diaphragm force generation in dogs that are hypercapnic and hypoxic [3]. These findings suggest that aminophylline is capable of exerting a positive inotropic effect during hypoxia or hypercapnia, but the relevance to man is currently uncertain.

VIIRES *et al.* [21] have suggested from *in vitro* experiments that theophylline diffuses more easily into thin diaphragm strips than into a rat hemidiaphragm preparation. To ensure adequate penetration of the muscle core by theophylline we not only used very thin diaphragm strips, but also high concentrations of the drug. Our primary interest was in studying the effect of the drug on pHi, and not in trying to predict if it would work at non-toxic levels *in vivo*. Careful studies in man have not yet fully resolved the role of theophylline in the treatment of respiratory muscle fatigue [5].

Estimation of pHi from the distribution volumes of DMO is a well validated technique [15, 22, 23]. DMO and microelectrode techniques have been directly compared and found to give similar pHi results [22, 23]. At physiological extracellular pH we found diaphragm pHi to be 7.10, in accordance with the generally accepted value of approximately 7.0 for muscle [14, 15]. Although intracellular acidosis can occur with muscle fatigue [24], it is not invariably associated [9, 25]. RENAUD *et al.* [26] found that the reduction in pHi in fatigued frog muscles was insufficient to account for the force loss. In our fatigued preparations pHi was unchanged, suggesting that mechanisms other than acidosis were producing the low frequency fatigue. In fatigued muscles treated with aminophylline, TT returned to control levels despite the development of a significant intracellular acidosis) (fig. 2).

Hypercapnia markedly reduced diaphragm pHi. Hypoxia also lowered pHi, but the degree of intracellular acidosis was not sufficient to account for the force loss [13]. Following the various perturbations, there was no simple relationship between TT and pHi. Hypercapnia caused the greatest intracellular acidosis, but depressed the twitch less than did electrical fatigue or hypoxia (fig. 2). RENAUD *et al.* [26] similarly found that hypercapnia lowered pHi more than did fatigue, although force loss was greater with the latter. The improvement of force generation in our fatigued and hypoxic muscles was associated with a significant fall in pHi (fig. 2). As this aminophylline-associated reduction in pHi was not seen in resting (unstimulated) diaphragms it is possible that the increase in force production was obtained at the expense of increased muscle oxygen consumption or increased substrate utilization. There is little information on the effect of xanthines on pHi. CONNETT [12], using the DMO technique, found that 2.0 mmol·l^{-1} theophylline caused a marked intracellular alkalosis in isolated frog sartorius muscle. Connett attributed the alkalinization to elevated internal free calcium, as it was prevented by agents that block calcium release from the sarcoplasmic reticulum. Our results show that an increase in pHi is not the cause of theophylline-induced twitch potentiation in mammalian skeletal muscle.

Intracellular acidosis is usually associated with reduced contractility [13, 24–26], and it is therefore unlikely that the fall in pHi seen in aminophylline-treated muscles caused the twitch recovery. Rather, it is likely that aminophylline improved TT by an effect independent of pHi, and that the stronger contractions increased acid accumulation and decreased pHi. It is not known if this would occur *in vivo*, where blood flow "washes out" the acid byproducts of metabolism. During

contraction, diaphragm blood flow increases, and aminophylline because of its vasodilator effect might further increase this flow. To our knowledge, there are no data on the effect *in vivo* of fatigue or aminophylline on diaphragm pHi.

The mechanism by which xanthines improve contractility is uncertain; it is probably not due to phosphodiesterase inhibition [7] or adenosine blockade [27] but, with high concentrations, might be associated with increased calcium release from the sarcoplasmic reticulum [10]. Our results show that high dose aminophylline improves TT in diaphragms that are fatigued, hypercapnic or hypoxic. The twitch-potentiation is not mediated by induction of an intracellular alkalosis. Indeed, high dose theophylline improved diaphragm contractility despite causing a fall in pHi. Stimulation was not continued for long enough to say whether this intracellular acidosis might ultimately be deleterious, but in this connection it is interesting that a recent report suggests that theophylline itself might promote muscle fatigue [28].

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Effet de l'aminophylline sur la fonction et sur le pH intracellulaire du diaphragme de rat. C.D. Shee, A.M. Wright, I.R. Cameron.

RÉSUMÉ: Nous avons étudié les effets de l'aminophylline sur la tension "par à-coups" et sur le pH intracellulaire (pHi) de lambeaux diaphragmatiques isolés du rat, qui était fatigué, hypercapnique ou hypoxique. Les muscles perfusés ont été stimulés directement à 0.5 Hz. Le pHi a été mesurè à partir des volumes de distribution de la dimethyl-oxazolidinedione. La fatigue a été induite par une stimulation tétanique intermittente. L'hypercapnie et l'hypoxie ont été produites en modifiant la Pco_2 et la Po_2 du superfuseur. L'aminophylline (1.0 mmol·l^{-1}) a inversé la chute des contractions observées

pendant la fatigue ou l'acidose hypercapnique, et a entraîné une récupération partielle de la dépression des contractions pendant l'hypoxie. La fatigue musculaire n'était pas due à une acidose intracellulaire. Tant l'hypercapnie que l'hypoxie ont fait baisser le pH. L'aminophylline n'a pas modifié le pHi dans les muscles non stimulés, mais a causé une chute significative du pHi dans les muscles stimulés qui étaient fatigués ou hypoxiques. De fortes doses d'aminophylline ont augmenté la tension de contraction dans les lambeaux diaphragmatiques fatigués, acidotiques ou hypoxiques. La potentiation contractile n'était pas due à l'alcalose intracellulaire. L'aminophylline a fait baisser le pHi dans les muscles stimulés, et donc pourrait parfois théoriquement être défavorable dans le traitement de la fatique musculaire.
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