LIMITATIONS TO PERFORMANCE AND MALLEABILITY OF THE SYSTEM

J. exp. Biol. **115**, 307–318 (1985)
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METABOLIC AND CIRCULATORY LIMITATIONS TO MUSCULAR PERFORMANCE AT THE ORGAN LEVEL

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SUMMARY

Within working muscle, development of conditions that directly influence exercise performance is dependent on many factors, including: intensity and duration of exercise, type of skeletal muscle fibres recruited, cardiovascular support to the working fibres and the inherent metabolic characteristics of the contracting fibres. In general, it is possible to identify factors that seem to alter exercise performance only at relatively intense exercise conditions. During prolonged moderately intense exercise (e.g. 70–80% maximal oxygen consumption for at least 60–90 min) decline in performance is related to the depletion of glycogen within the working muscle. Although the cause of muscle performance decline during very intense exercise is not known, an extreme acidosis is found, especially in fast-twitch muscle, which could significantly disrupt normal metabolic and contractile processes. During fatigue caused by intense contraction conditions, ATP content decreases (by approx. 50%) and there is a stoichiometric production of IMP and ammonia in fast-twitch muscle. This loss in adenine nucleotide content is dependent on the severity of the contraction conditions relative to the functional aerobic capacity of the muscle fibre, since fast-twitch red (high mitochondria, high blood flow) and fast-twitch white (low mitochondria, low blood flow) muscles respond differently. In contrast, during similarly intense contraction conditions, rat slow-twitch muscle fibres maintain their ATP content and do not produce significant amounts of IMP. Indirect evidence suggests that a similar contrast between fibres occurs in humans during maximal exercise. Thus, there seems to be a fundamental difference between fast- and slow-twitch muscles in the management of their adenine nucleotide contents during intense contraction conditions. Whether this is related to the known differences in the fatigue process between these fibre types is not known.

INTRODUCTION

The intensity and duration of exercise, the type of skeletal muscle fibres recruited (including their respective cardiovascular support) and the inherent metabolic

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Key words: Fatigue, muscle fibre type, ATP, IMP, ammonia, oxidative capacity.

characteristics of the contracting fibres directly influence exercise performance in working muscle. It is generally difficult to identify any factor that directly affects muscle performance when the exercise intensity is rather mild. Thus, when the exercise intensity is well below 50 % of the maximal aerobic capacity, exercise can be sustained for many hours and the inability to continue exercise may be related to central and/or non-muscle metabolic events that detract from the general sense of well-being. In contrast, when the exercise intensity is increased to about 70–80 % of maximal aerobic capacity, fatigue to the point of failure (defined as a decline in tension or work output) seems to be directly related to substrate supply within the muscle. This limitation, however, can be influenced by metabolic factors external to the muscle. Finally, when the muscle contraction conditions become extremely intense, metabolic events within the muscle can lead to a direct loss of muscle performance.

PROLONGED FAIRLY INTENSE EXERCISE

During fairly intense exercise (approximately 70–80 % max V_{O_2}), which can be maintained for at least 60–90 min in highly motivated individuals, the inability to continue exercise at the same work intensity corresponds to depletion of glycogen within the working muscle. This apparent dependence on stored carbohydrate has been long recognized (Milvy, 1977; Pernow & Saltin, 1971; Porter & Whelan, 1981). Since energy expenditure at this exercise intensity is submaximal and muscle blood flow and oxygen extraction are fairly constant over time (Saltin *et al.* 1976), it is doubtful that an inadequate oxygen delivery is the determining factor. Rather, it is events within the working muscle that, for some unknown reason, require a sustained rate of glycogen utilization. Thus, when the internal glycogen stores are nearly depleted, the work rate cannot be maintained (Saltin & Karlsson, 1971). Further, it is apparent that differences in the quantity of muscle glycogen available at the onset of exercise can influence the duration of exercise (Hultman, 1967). Hultman and Bergstom (see Hultman, 1967) varied the initial muscle glycogen concentration over a four-fold range (½ to 2 times normal) and found a direct relationship with the time to exhaustion. Thus, a greater muscle glycogen store in the working muscle leads to a greater capacity for endurance exercise. The importance of muscle glycogen for exercise performance is also seen from experiments designed to reduce the rate of glycogen utilization during a given exercise effort. Hickson *et al.* (1977) found an enhanced endurance capacity in rats when the rate of muscle glycogen utilization was reduced by elevating the circulating free fatty acid concentration. This resulted in a higher glycogen content at any given time in the exercise bout. However, at the point of exhaustion, muscle glycogen was depleted to the same degree as during the control situation. A similar result has been found in humans (Costill *et al.* 1977) and probably represents a general mammalian response. Finally, if the rate of glycogen utilization is reduced, as found after training, there is an enhanced endurance performance. Again, the sparing of glycogen can be attributed to a greater rate of fatty acid oxidation (in this case probably due to the higher mitochondrial content in the trained muscle, Holloszy & Coyle, 1984). Thus, factors that promote glycogen retention within the muscle

extend exercise performance. It is important to recognize that the impact of muscle glycogen content in limiting muscle performance is relegated to exercise situations where the metabolic stress is extensive (e.g. 70–80 % max V_{O_2}), but can be sustained for a prolonged time (e.g. at least 60–90 min). Although glycogen is utilized faster in more intense exercise, the duration of exercise is abbreviated and fatigue is not associated with depletion of glycogen stores (Saltin & Karlsson, 1971).

SHORT-TERM INTENSE EXERCISE

During intense muscle contraction conditions, that can be maintained for only a brief time, local factors within the muscle appear to be responsible for the loss in performance. However, the time course of the fatigue response may be influenced by external factors (e.g. cardiovascular supply of oxygen). Further, it is probable that inherent biochemical characteristics, unique to a given muscle fibre type, establish a heterogeneity in the fatigue response. This probably accounts for the extremely different fatigue responses for the different types of motor units identified by Burke *et al.* (1971). Although it is not possible to identify a single factor that explains the molecular basis of fatigue, extensive characterization of the cellular environment has suggested several factors that could be responsible for the failure in muscle performance during intense contraction conditions.

One major factor that alters the intracellular environment during intense contraction conditions is the decrease in pH. This appears to be directly related to the increase in muscle lactic acid content (Sahlin, Harris & Hultman, 1978), and is caused by the greatly accelerated rate of glycogenolysis. The increased H^+ concentration has a number of consequences. A decrease in sarcoplasmic pH increases the Ca^{2+} requirement for tension development (Donaldson & Hermansen, 1978) and diminishes the peak muscle tension possible (Fabiato & Fabiato, 1978). This could account for the decline in tension that is directly related to the degree of acidosis (Dawson, Gadian & Wilkie, 1978). Acidosis is also expected to reduce the rate of glycolysis by decreasing the activity of phosphofructokinase (Trivedi & Danforth, 1966). During intense isometric contraction conditions the rates of energy expenditure and glycolysis can be exceptionally high. However, as fatigue develops there should be a decrease in energy expenditure, since the energy demands of contraction are directly related to the tension developed (Kushmerick & Paul, 1976). Thus, the decline in glycolytic ATP provision may be of secondary consequence. The decline in rate of glycolysis may be protective by limiting the acidotic and osmotic load within a muscle that is already failing.

Although it is generally apparent that the muscle ATP content is not depleted during the fatigue process, it is clear that a significant decrease in ATP concentration can occur in fast-twitch muscle. The decline in ATP does not result in a stoichiometric increase in ADP or AMP content, but to a loss of total adenine nucleotides (TAN = ATP + ADP + AMP) that occurs by the deamination AMP to IMP and NH_3 (Lowenstein, 1972). The rate of AMP deamination is extremely low in resting muscle, probably due to the low free AMP content and inhibition by orthophosphate

(Wheeler & Lowenstein, 1979). However, as shown in Fig. 1, during periods of severe metabolic stress the enzyme becomes activated, reduces the ATP content by approximately 50 % and produces a stoichiometric increase in tissue ammonia content and a 70- to 90-fold increase in the muscle's IMP content (Meyer & Terjung, 1979). Coincident with the deamination of AMP is an extreme loss of tension development, a near depletion of phosphocreatine and a high lactic acid content (Fig. 1). Evidence suggests that this attendent acidosis is an important factor in modifying AMP deaminase activity (Wheeler & Lowenstein, 1979; Dudley & Terjung, 1984*b*). Return of the ATP content in the muscle occurs by reamination of IMP during the recovery period (Meyer & Terjung, 1979, 1980). There is no apparent relationship (see Fig. 2) between the recovery of TAN content and the recovery of tension development in the 20-min period following contractions.

Although the significance of this AMP deamination has not been established, the decrease in TAN content should help limit the decrease in the ratio of ATP to ADP in the contracting muscle and, thereby, the decrease in the free energy of ATP hydrolysis (Lowenstein, 1972). This would occur by removing one product of the myokinase reaction (AMP), thereby 'driving' the reaction towards ATP production, and could be important in maintaining cell viability by protecting the cell from an extremely energy-depleted state. In addition, the accumulation of IMP provides a

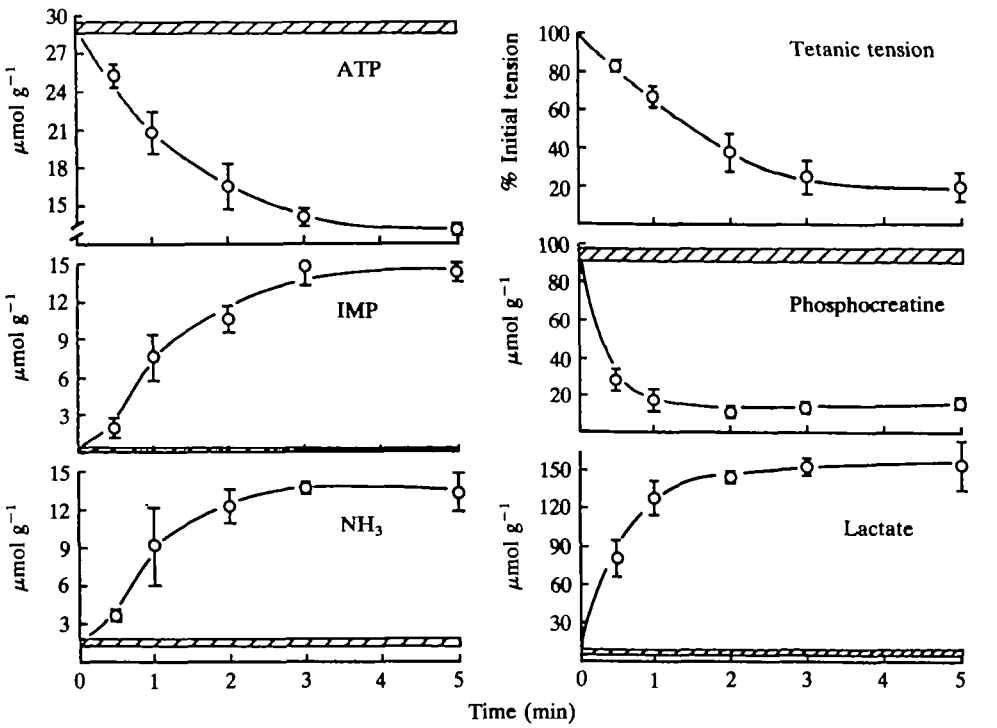

Fig. 1. Decline in tension and changes in metabolite contents (in μmol g^{-1} dry weight) in rat fast-twitch muscle during contractions at 60 tetani min^{-1}. Reproduced from Meyer & Terjung, 1979 with permission.

pool of purine nucleotide that remains within the muscle cell and, therefore, available for reamination to recover the adenine nucleotide pool (Meyer & Terjung, 1979). Recovery of adenine nucleotide content in this manner would not require an extensive increase in *de novo* purine synthesis and/or purine salvage pathway activity.

The decline in ATP content to only approximately 50% is not due to the unavailability of the total ATP pool within the muscle, since as shown in Fig. 3, contracting muscle poisoned with iodoacetic acid will deaminate 85–90% of the muscle's ATP to yield a stoichiometric increase in IMP content (Dudley & Terjung,

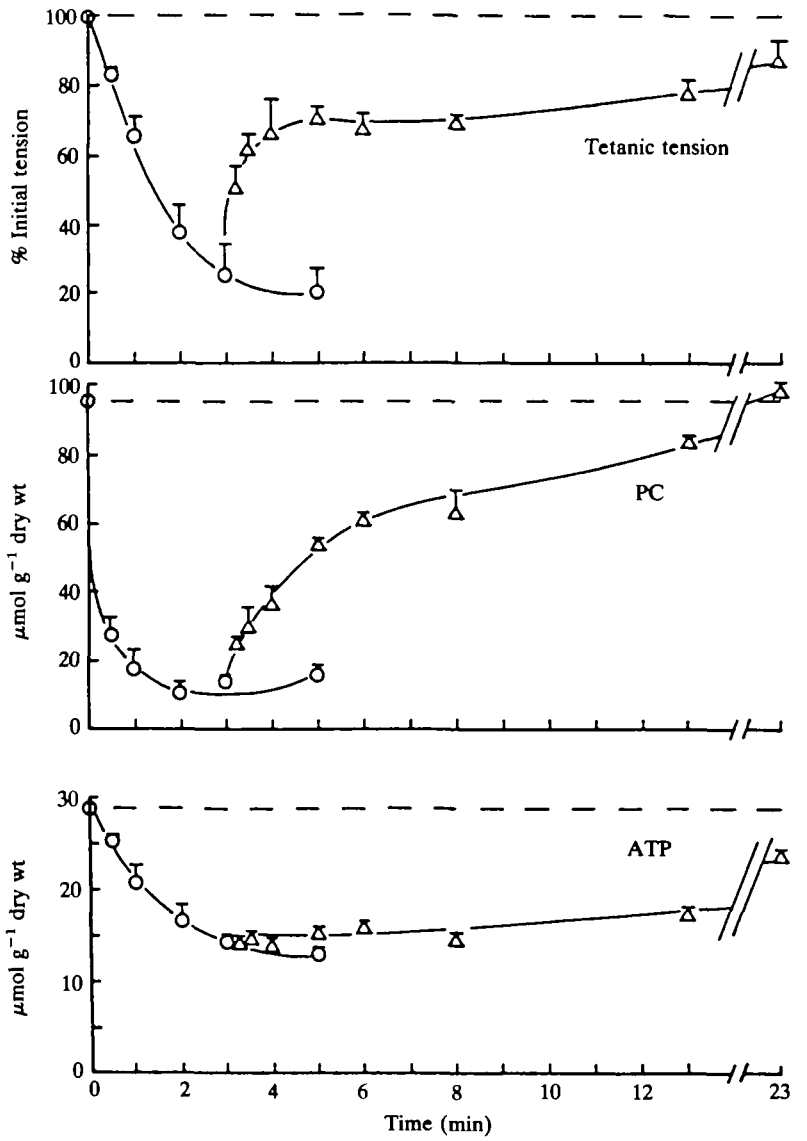

Fig. 2. Recovery of tension development, phosphocreatine (PC) and ATP in fast-twitch rat gastrocnemius muscle following contractions at 60 tetani min^{-1}. (○) stimulation; (△) recovery.

1985*b*). It is reasonable to interpret the loss of ATP and the accumulation of IMP as reflecting an imbalance between ATP hydrolysis and ADP phosphorylation in the cell. In this context, the extent of the ATP decrease may simply reflect a condition when the excessive rate of ATP hydrolysis has lessened, owing to the extensive reduction in tension development (Fig. 1). Whether the imbalance between ATP supply and demand is directly related to the cause of contraction malfunction has not been established. However, the lack of IMP production, resulting in an inordinate increase in free ADP, would be expected significantly to affect muscle relaxation properties (Dawson, Gadian & Wilkie, 1980).

In contrast to the response in fast-twitch muscle, intense tetanic contractions by the rat slow-twitch muscle did not accelerate AMP deaminase activity (Meyer & Terjung, 1979). Although there was an extensive loss of tension development, ATP content remained at approximately 90 % of rest and there was no detectable IMP accumulation (Fig. 4). Interestingly, phosphocreatine content declined by approximately 60 % and lactic acid content increased modestly. Even when blood flow was eliminated, resulting in a total loss of tension development, the ATP content remained at approximately 90 % of normal. Thus, the rate of AMP deaminase activity could not be significantly increased in the slow-twitch muscle fibre. Even though this fibre type contains a lower peak activity of AMP deaminase (Winder, Terjung, Baldwin & Holloszy, 1974) and the enzyme may be subject to quantitatively different

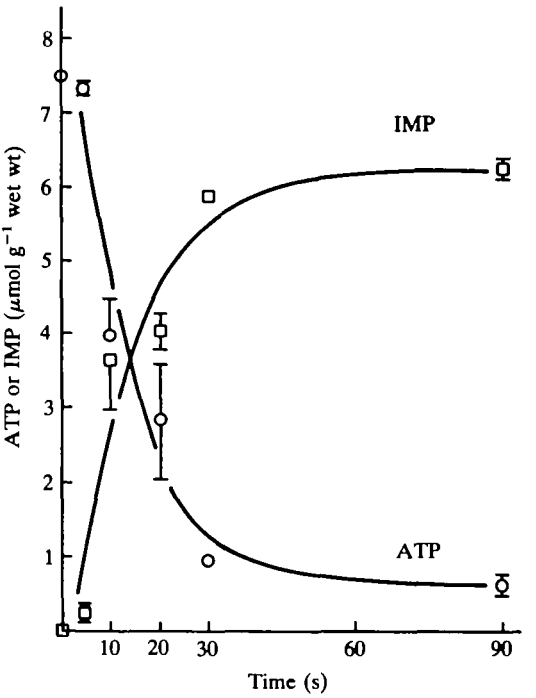

Fig. 3. Depletion of ATP content and increase in IMP content in contracting (5-Hz twitch) fast-twitch muscle poisoned with iodoacetic acid. Data taken from Dudley & Terjung, 1985*b*.

modifying influences (Waarde & Kesbeke, 1981), the failure significantly to activate AMP deaminase was probably due to the lack of development of cellular conditions necessary to activate the enzyme. An 80% reduction in ATP content and a stoichiometric increase in IMP content can be achieved in iodoacetic acid poisoned slow-twitch rat muscle (Table 1; D. M. Whitlock & R. L. Terjung, unpublished observations). Thus, there is a fundamental difference in the management of adenine nucleotides between fast-twitch and slow-twitch muscle during excessive metabolic stress caused by intense contraction conditions. It may be concluded that the loss of contractile function in slow-twitch rat muscle is due to a lesion in a critical process, possibly associated wih excitation-contraction coupling, without depleting a large fraction of the ATP pool within the cell. It is unlikely that severe acidosis, similar to that seen in fast-twitch muscle, contributes to this fatigue, since the lactic acid content increased to only 12–14 μmol g^{-1} wet weight. Further, this lesion in slow-twitch muscle is exquisitely sensitive to aerobic energy provision. Complete tension loss occurs after eliminating blood flow, whereas full recovery of tension is established within 1 min after reinstating normal blood flow (Meyer & Terjung, 1979).

It is also clear that all fast-twitch muscle does not respond in an identical manner during extensive metabolic stress. Indeed, the inherent differences in the functional capacity for aerobic metabolism significantly influence whether the adenine nucleotide content can be maintained during high-frequency contractions. This is apparent by following the time course of response to 5-Hz twitch contractions in fast-twitch white (FTW; low mitochondria, low blood flow) and fast-twitch red muscle (FTR; high mitochondria, high blood flow) muscle. The FTW muscle is unable to maintain an adequate energy balance and suffers a 50% loss of TAN and a stoichiometric increase in IMP content (Dudley & Terjung, 1985*a*) (Fig. 5). The response was identical to that found during intense tetanic contraction conditions (Meyer & Terjung, 1979). In contrast, FTR muscle fibres of the same contracting muscle (gastrocnemius) were able to continue the 5-Hz contractions without significant activation of AMP deaminase. One major difference in the response between these two muscle fibre sections was the low lactate content in the FTR (13+1·3 μmol g^{-1}) compared to the FTW (43+3·5 μmol g^{-1}). The extreme acidosis in the FTW section probably contributed to the activation of AMP deaminase

Table 1. *Activation of AMP deaminase in contracting iodoacetic acid poisoned rat slow-twitch red muscle (soleus)*

	ATP (μmol g^{-1})	IMP (μmol g^{-1})	NH_4 (μmol g^{-1})	Lactate (μmol g^{-1})
Control (non-stimulated)	3·75 ± 0·16 (5)	0·18 ± 0·02 (5)	0·83 ± 0·21 (5)	2·12 ± 0·10 (5)
Stimulated (in presence of iodoacetic acid	0·77 ± 0·12 (5)	3·16 ± 0·21 (5)	3·79 ± 0·26 (5)	3·18 ± 0·73 (5)

Soleii were stimulated for 5 min at 120 tetani min^{-1} (Meyer & Terjung, 1979) after exposure to iodoacetic acid as described by Dudley & Terjung (1985*b*).

(Dudley & Terjung, 1985*b*). This ability of the FTR muscle to accommodate the metabolic stress was directly dependent on muscle blood flow (Fig. 6). When blood flow was eliminated just prior to contractions, the FTR muscle section suffered an extreme acidosis, a 50% loss of ATP and a stoichiometric increase in IMP content (Dudley & Terjung, 1985*a*). Thus, removal of the inherently greater capacity for

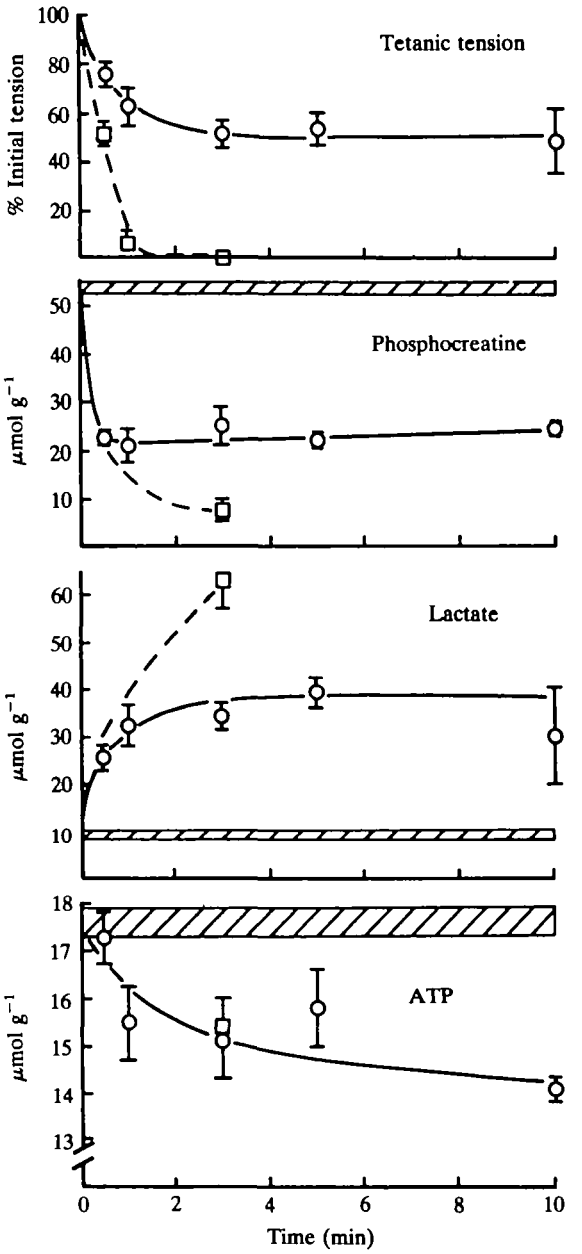

Fig. 4. Decline in tension and changes in ATP, phosphocreatine and lactate content (in μmol g^{-1} dry weight) in rat slow-twitch muscle (soleus) during contractions (120 tetani min^{-1}). (○) Blood flow intact; (□) blood flow occluded. Reproduced from Meyer & Terjung, 1979 with permission.

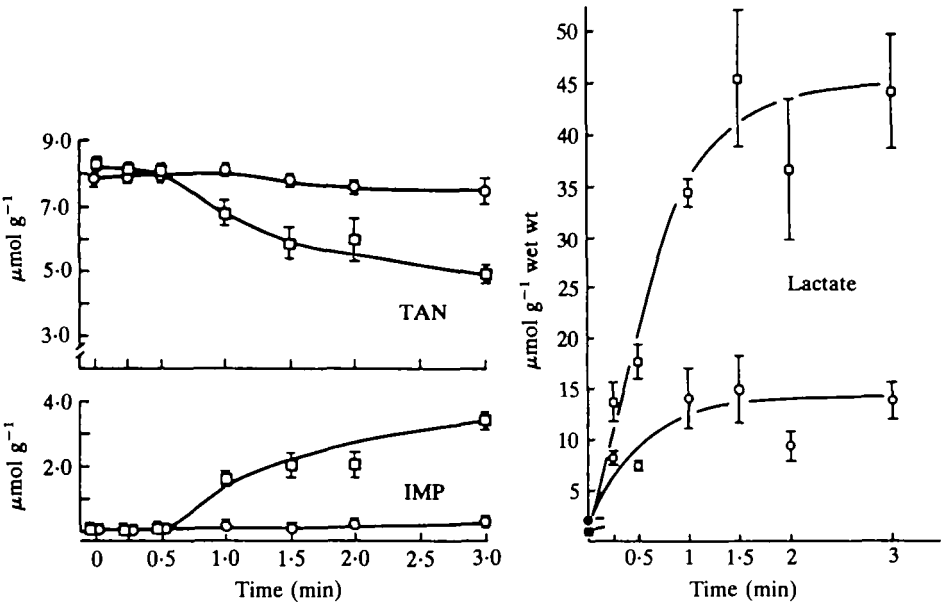

Fig. 5. Total adenine nucleotide (TAN = ATP + ADP + AMP), IMP and lactate contents in fast-twitch white (□) and fast-twitch red (○) gastrocnemius muscle during 5-Hz twitch contractions with blood flow intact. Data taken from Dudley & Terjung, 1985*a*.

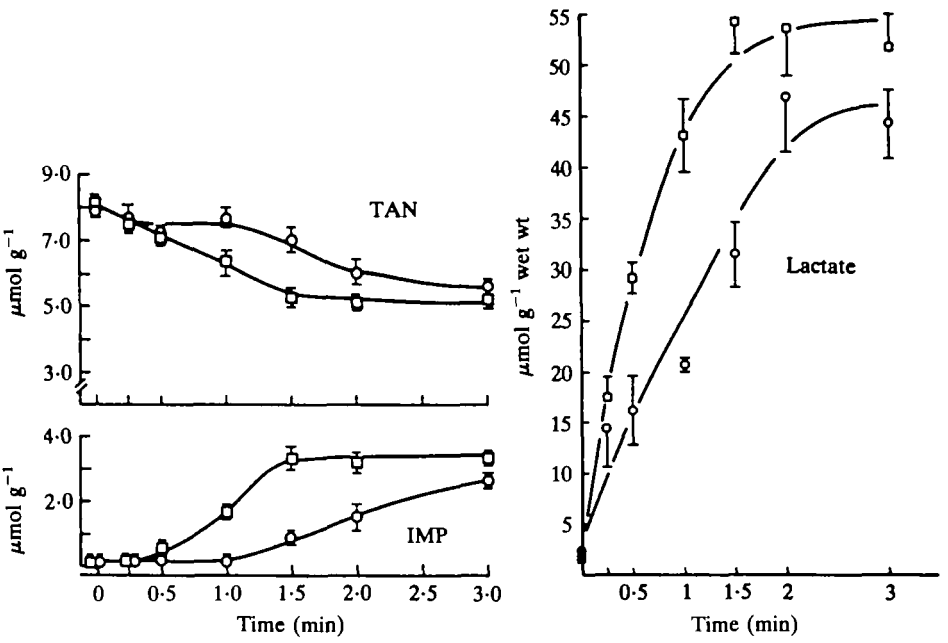

Fig. 6. Total adenine nucleotide (TAN = ATP + ADP + AMP), IMP and lactate contents in fast-twitch white (□) and fast-twitch red (○) gastrocnemius muscle during 5-Hz twitch contractions with blood flow occluded. Data taken from Dudley & Terjung, 1985*b*.

aerobic metabolism caused the two fast-twitch muscles to respond similarly, indicating that the capacity for energy provision (especially mitochondrial respiration) greatly influences the ability of muscle to sustain contractions with an excellent energy balance. This was further illustrated in the response of FTW muscle from trained animals (Fig. 7). The training programme employed increased the

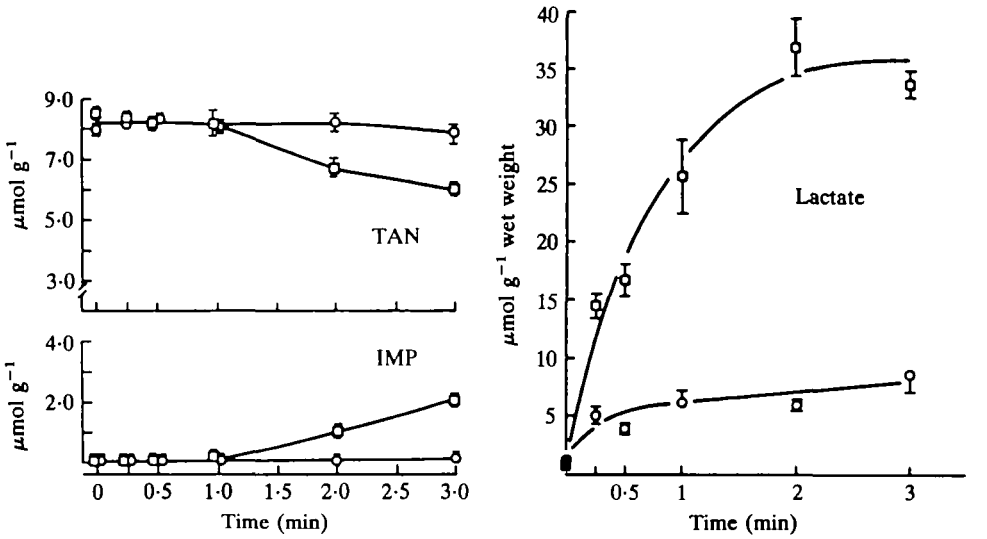

Fig. 7. Total adenine nucleotide (TAN = ATP + ADP + AMP), IMP and lactate contents in fast-twitch white (□) and fast-twitch red (○) gastrocnemius muscle of exercise-trained rats during 5-Hz twitch contractions with blood flow intact. Data taken from Dudley & Terjung, 1985*a*.

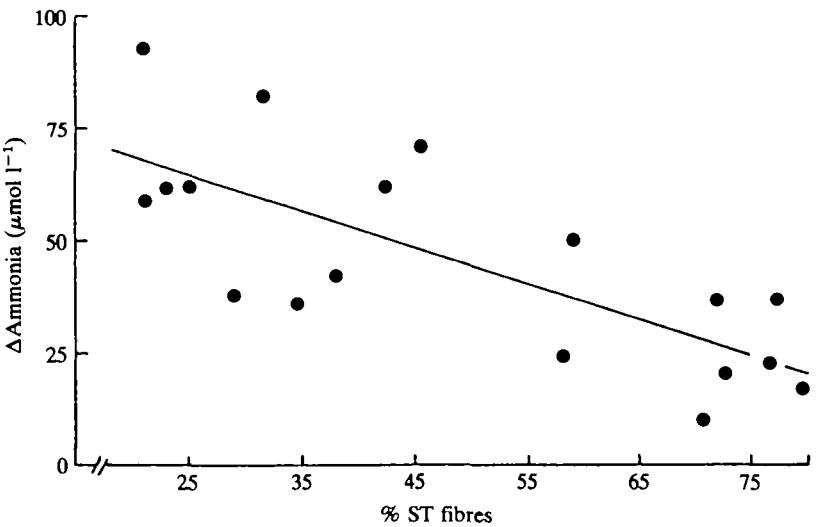

Fig. 8. Relationship between percentage of slow-twitch (ST) fibres and increase in blood ammonia concentration after maximal exercise in humans. Reproduced from Dudley *et al.* 1983 with permission. $r = -0{\cdot}75$; $y = 0{\cdot}799x + 84{\cdot}75$.

mitochondrial content (150 %) and blood flow capacity (40–50 %) in this fibre section (Mackie & Terjung, 1983). Evidence for an improvement in the functional aerobic capacity of this muscle section is seen in the smaller decrease in ATP content and the smaller increase in IMP content during 5-Hz contractions. Thus, the ability of fast-twitch muscle to sustain contractions with an excellent energy balance seems to be a function of the metabolic stress relative to the ability of the muscle to accommodate the energy demands of contractions.

The contrasting response of the different fibre types during contractions emphasizes one complexity in evaluating the functional and metabolic response of muscle. This heterogeneity could lead to a significant error in interpreting data obtained from muscles containing a mixture of fibre types, depending on the contrast in fibre type response established by the particular contraction conditions. Thus, as is now generally recognized, it is important to consider the metabolic response unique to each skeletal muscle fibre type (Hintz *et al.* 1982).

Although much of the information concerning ATP depletion is obtained from isolated muscle preparations, *in vivo* exercise conditions with humans (Sahlin, Palmskog & Hultman, 1978; Sutton, Toews, Ward & Fox, 1980), rats (Meyer, Dudley & Terjung, 1980) and fish (Driedzic & Hochachka, 1976) have demonstrated a significant IMP production. Further, data have been obtained from rodents after intense treadmill running that are consistent with the different management of adenine nucleotides in fast-twitch and slow-twitch fibres (Meyer *et al.* 1980). It is unclear whether this distinction also exists in humans. Circumstantial evidence, however, is available . Dudley *et al.* (1983) found a direct linear relationship between the increase in blood ammonia during intense exercise and the percentage of fast-twitch muscle fibres in their subjects (Fig. 8). This may be characteristic of a general distinction between fast- and slow-twitch muscle fibre types in their management of the adenine nucleotide pool during intense muscle contractions.

Work from the authors' laboratory was supported by National Institutes of Health Grant AM–21617 and Research Career Development Award AM–00681.

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