METABOLIC HETEROGENEITY OF MUSCLE FIBRES

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SUMMARY

Mammalian skeletal muscle is an extremely heterogeneous tissue. Its diversity results from a spectrum of fibres which are metabolically suited to a wide range of functional demands. As judged from enzyme activity analyses of single fibres, the metabolic properties of fibres belonging to the same motor unit are similar or identical. It is likely, therefore, that the phenotype expression of muscle fibres is primarily under neural control. Differences in recruitment patterns of various motor units explain the wide range of metabolic properties as evidenced by pronounced variations in enzyme activities and enzyme activity ratios. There exist large overlaps between the activity spectra of various enzymes of anaerobic and aerobic metabolism in slow- and fast-twitch fibres. Nevertheless, these two major fibre classes can be distinguished by discriminative enzyme activity ratios (e.g. phosphofructokinase/malate dehydrogenase, phosphofructokinase/3-hydroxyacyl-CoA dehydrogenase, fructose-1,6-diphosphatase/phosphofructokinase). Moreover, slow-twitch fibres display an H-type isozyme pattern of lactate dehydrogenase, whereas fast-twitch fibres are characterized by a predominance of LDH-5. No clear-cut differences exist between enzyme activity profiles and LDH isozyme patterns of the IIA and IIB subgroups of fast-twitch fibres. Comparative studies indicate that the metabolic properties of IIA and IIB fibres vary in different animal species. This observation supports the notion that metabolic and myosin-related properties of muscle fibres may be regulated independently. Due to relatively high turnover rates of enzymes of energy metabolism in muscle, changes in functional demands may be met by relatively rapid changes in metabolic properties. In view of these findings it is not surprising that muscle fibres display a spectrum of metabolic properties and represent stages within a dynamic equilibrium.

INTRODUCTION

Energy metabolism of muscle is qualitatively and quantitatively adjusted to specific functional requirements. Chief features of metabolic adaptation in muscle relate to the type of fuel used and to the metabolic capacities of anaerobic and aerobic pathways. Basically, these are determined by the set of enzymes present and their effective catalytic activities. Indeed, various metabolic types of muscle have previously been distinguished by enzyme activity pattern analyses (Vogell *et al.* 1959; Pette & Bücher, 1963; Bass *et al.* 1969; Pette, 1971).

ENZYME ACTIVITY PATTERNS

Tissue levels of enzyme activities determined under optimum conditions *in vitro* reflect enzyme concentrations. Although they cannot be set equal to effective flux rates *in vivo*, they may be used as relative measures of metabolic capacities. Comparative analyses of enzyme activity patterns revealed that certain enzyme activities exist in similar or constant proportions in various muscles independent of variations in absolute levels (Pette, 1965, 1966; Pette & Hofer, 1980). The order of enzymes in these constant proportion groups (e.g. of the glycolytic pathway or the citric acid cycle) reflects functional requirements. This is emphasized by the observation that constant proportions are maintained at experimentally induced alterations in absolute activities. In this context, changes in the enzyme activity patterns of muscles induced by cross-reinnervation (Golisch, Pette & Pichlmaier, 1970) or by chronic nerve stimulation (Pette, Smith, Staudte & Vrbová, 1973; Pette, 1984) are relevant examples.

In contrast to constant proportion groups, which reflect stable units of the enzyme activity pattern, other enzymes display variable or specific activity ratios. Such enzymes are found mainly at metabolic branch points, or in separate anabolic-catabolic segments of the same pathway. The activity ratios of these enzymes represent indicators of metabolic specialization (Pette, 1965; Staudte & Pette, 1972).

ENZYME ANALYSES OF SINGLE FIBRES

Mammalian muscles are composed of fast- and slow-twitch fibres. Qualitative enzyme histochemistry provided evidence that these two major fibre classes can be metabolically subdivided into further types. Barnard, Edgerton, Furukawa & Peter (1971) and Peter *et al.* (1972) distinguished slow-twitch-oxidative (SO), fast-twitch-glycolytic (FG), and fast-twitch-oxidative-glycolytic (FOG) fibre types.

The knowledge of metabolic specialization has been greatly advanced by the application of quantitative micromethods for enzyme activity measurements in single, microdissected fibres (Essén *et al.* 1975). Measurements of many enzymes in muscle fibres of the rat (Hintz *et al.* 1980; Nemeth, Pette & Vrobvá, 1981), the rabbit (Spamer & Pette, 1977, 1979, 1980) and the human (Lowry *et al.* 1978, 1980) revealed that neither fast- nor slow-twitch fibres are metabolically homogeneous. On the contrary, fast- and slow-twitch fibres represent two populations with wide activity ranges both of enzymes representing anaerobic or aerobic metabolic systems (e.g. Lowry *et al.* 1980; Spamer & Pette, 1980).

Fig. 1 shows activity levels of succinate dehydrogenase (SDH) which were determined microphotometrically in several hundred fibres in serial sections of human tibialis anterior muscle (Reichmann & Pette, 1982). It is obvious that slow- (type I) and fast-twitch (type II) fibres display wide ranges of activity. In spite of the overlap between type II and type I fibres, the majority of the latter is characterized by higher SDH activities as compared to the majority of the type II fibres. Within the

type II population fibres with high and fibres with low activities correspond to the FOG and FG types which represent extremes of a continuum. Finally, it is obvious from Fig. 1 that the actomyosin ATPase-based IIA and IIB fibre subgroups cannot be distinguished by SDH activity in human tibialis anterior.

ENZYME ACTIVITIES IN FAST- AND SLOW-TWITCH FIBRES

The differences between fast- and slow-twitch fibres are similar to those existing between the enzyme activity patterns of muscles that are predominantly composed of fast- or slow-twitch fibres (Pette & Bücher, 1963; Bass *et al.* 1969). Generally, slow-twitch fibres display lower activities of glycolytic enzymes than fast-twitch fibres (Essén *et al.* 1975; Spamer & Pette, 1977, 1979, 1980; Lowry *et al.* 1978). However, there exist wide activity ranges of glycolytic enzymes in both fibre populations. This holds true also for enzyme activities representing standard functions of aerobic substrate oxidation, such as the mitochondrial enzymes of the citric acid cycle, or of fatty acid oxidation. As seen for succinate dehydrogenase in Fig. 1, these enzymes tend to have higher activities in slow- than in fast-twitch fibres in human muscle, but there exist large overlaps between the two fibre classes. The wide activity spectra of these mitochondrial enzymes and the overlaps between the two fibre populations makes it difficult to distinguish individual fast- and slow-twitch fibres. Therefore, measurement of these enzyme activities in muscle homogenates provides more information about metabolic characteristics of a given muscle than microbiochemical analyses on a limited number of single fibres.

The study of metabolic characteristics of muscle fibres is facilitated by measuring several enzymes in the same fibre in order to compare activity ratios. An example is
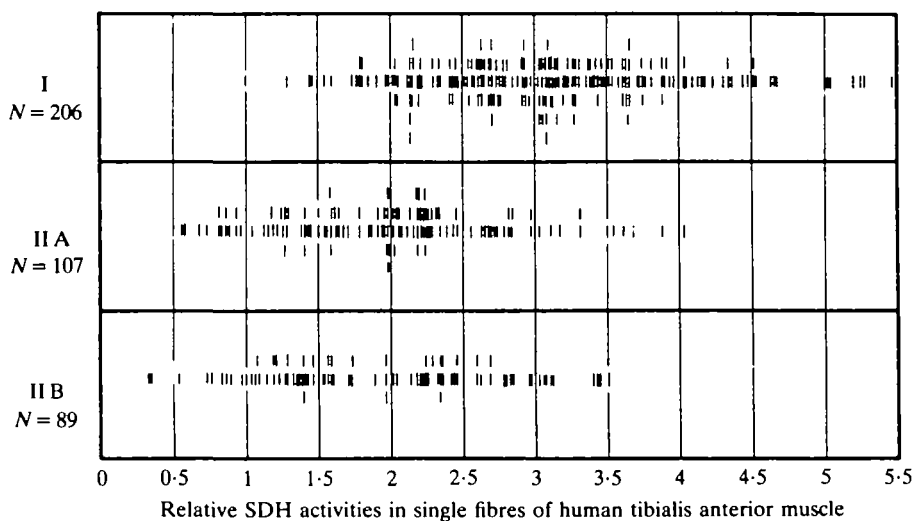

Fig. 1. Microphotometrically determined activity of succinate dehydrogenase (SDH) in type I, IIA and IIB fibres of human tibialis anterior muscle. Results from Reichmann & Pette (1982).

given in Fig. 2, in which the activity of phosphofructokinase (PFK) in individual fast- and slow-twitch fibres has been plotted against the activity of malate dehydrogenase (MDH) in the same fibres. In spite of large overlaps in MDH activity and wide PFK activity ranges, the two populations are clearly separated by this plot. The activity quotient PFK/MDH may thus be regarded as a discriminative marker. Indeed, this ratio between a glycolytic enzyme and an enzyme primarily related to the citric acid cycle represents a system correlation relevant to the two main pathways for anaerobic and aerobic energy supply. Similarly, fast- and slow-twitch fibres are distinguished by significant differences in the activity quotient phosphofructo-kinase/3-hydroxyacyl-CoA dehydrogenase. On the contrary, no distinction of the two populations is possible on the basis of activity ratios reflecting the correlation between fatty acid oxidation and the citric acid cycle. Malate dehydrogenase and 3-hydroxyacyl-CoA dehydrogenase activities are highly correlated (correlation coefficient: 0·74) in type I and II fibres (Spamer & Pette, 1980). The strict correlation of these two metabolic systems is evident also from comparative studies on different muscles (Staudte & Pette, 1972).

Among others (e.g. lactate dehydrogenase/citrate synthetase, hexokinase/ phosphofructokinase), the ratio between phosphofructokinase and fructose-1,6-
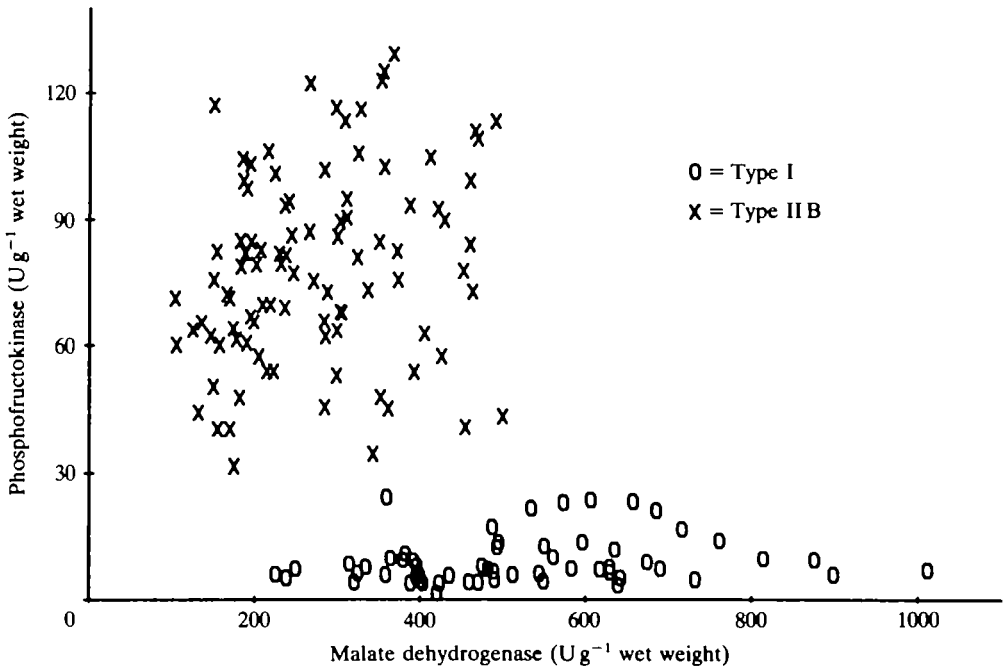

Fig. 2. Plot of phosphofructokinase against malate dehydrogenase activities as determined in individual fast (X) and slow-twitch (0) fibres of rabbit psoas and soleus muscles. Results from Spamer & Pette (1980).

diphosphatase (FDPase) activities represents another discriminative marker. FDPase, which catalyses the reverse reaction of PFK, is present at considerable activity in fast-twitch but is scarcely detectable in slow-twitch muscles (Krebs & Woodford, 1965; Opie & Newsholme, 1967; Bass *et al.* 1969). This type of distribution was confirmed for fast- and slow-twitch fibres of rabbit muscles (Spamer & Pette, 1980). Moreover, the two fibre types form distinct groups when classified according to their FDPase/PFK quotients. Neither in fast- (Fig. 3) nor in slow-twitch fibres exists a correlation between these two enzyme activities. This finding is relevant in view of the suggested role of FDPase together with PFK in a substrate cycle for regulating glycolytic flux rate (Newsholme & Crabtree, 1970). The lack of correlation between the two enzymes is difficult to reconcile with such a function. It is more conceivable that varying activity levels of FDPase reflect differences in gluconeogenic capacities.

LACTATE DEHYDROGENASE ISOZYME PATTERNS

As was recently shown by capillary electrophoresis of single fibres from rabbit muscles, marked differences exist between the isozyme complement of lactate
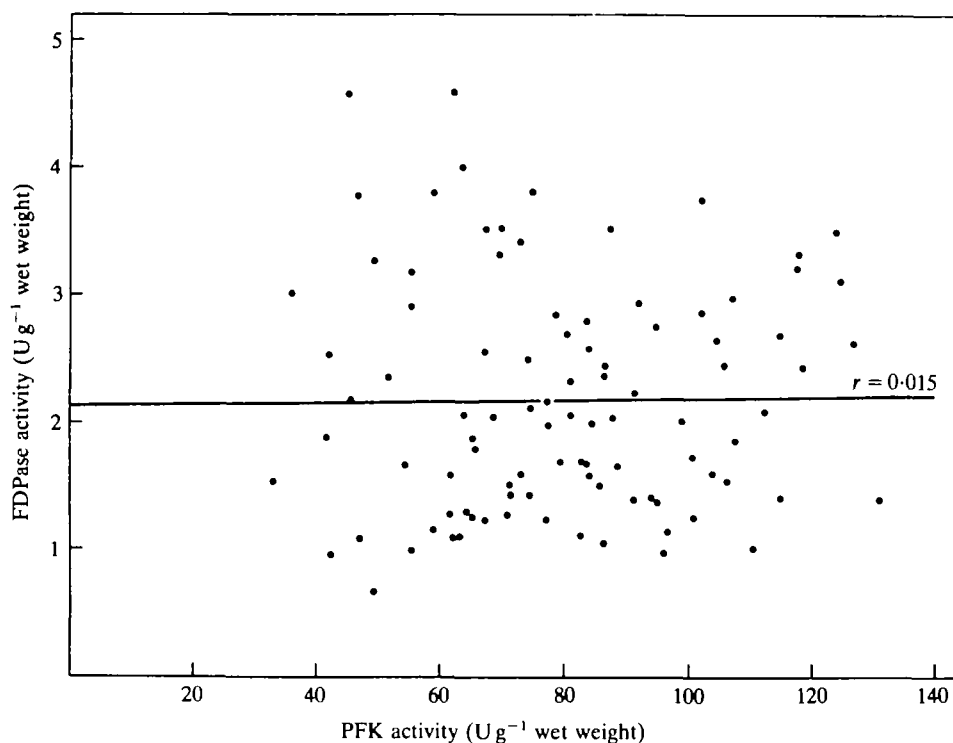

Fig. 3. Plot of fructose-1,6-diphosphatase (FDPase) against phosphofructokinase (PFK) activities in fast-twitch fibres of rabbit psoas muscle. Results from Spamer & Pette (1980).

dehydrogenase (LDH) in fast- and slow-twitch fibres (Leberer & Pette, 1984). Type I fibres are characterized by a unique pattern of all five LDH isozymes, with a predominance of LDH-1, 2 and 3. The majority (80 %) of type II fibres contains only LDH-5 (Fig. 4). About 20 % of the fast-twitch fibres contain, in addition to LDH-5 as the main component, small amounts of LDH-4 and 3 (Fig. 4). Interestingly, a correlation between these two types of LDH isozyme distributions exists neither for histochemically defined IIA and IIB subtypes nor for FG or FOG fibre types (Leberer & Pette, 1984).

METABOLIC PROPERTIES OF IIA AND IIB FIBRES

Brooke & Kaiser (1970) distinguished subtypes of fast-twitch fibres by differences in acid stability of myofibrillar actomyosin ATPase. Essén *et al.* (1975), who performed measurements of PFK and SDH activities in pooled type IIA and IIB fibres from human muscle, suggested a higher aerobic-oxidative capacity of type IIA than IIB fibres. However, Essén-Gustavsson & Henriksson (1983) have recently
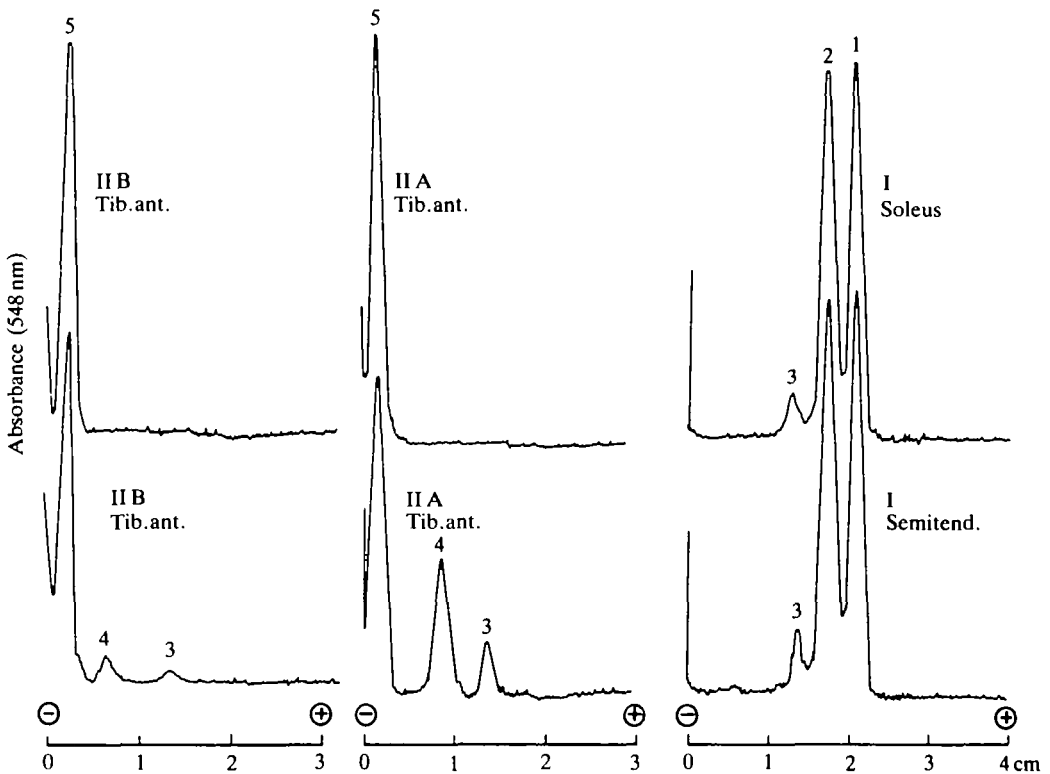

Fig. 4. Densitographs of microelectrophoreses for lactate dehydrogenase isozymes in single, histochemically typed fibres from rabbit muscles. From Leberer & Pette (1984). Tib. ant. = tibialis anterior muscle; Semitend. = semitendinosus muscle.

reported that no differences exist between activities of citrate synthetase and 3-hydroxyacyl-CoA dehydrogenase of pooled IIA and IIB fibres in the human. These latter findings are in agreement with results from qualitative (Sjøgaard, Houston, Nygaard & Saltin, 1978) and quantitative (Fig. 1) enzyme histochemistry on human muscle fibres (Reichmann & Pette, 1982).

Fig. 5 illustrates the profile of succinate dehydrogenase activity in histochemically typed IIA and IIB fibres of tibialis anterior muscles in rat and mouse. These and other results (Nemeth, Hofer & Pette, 1979; Nemeth & Pette, 1981; Reichmann & Pette, 1982, 1984b) do not support the notion that the distribution of succinate
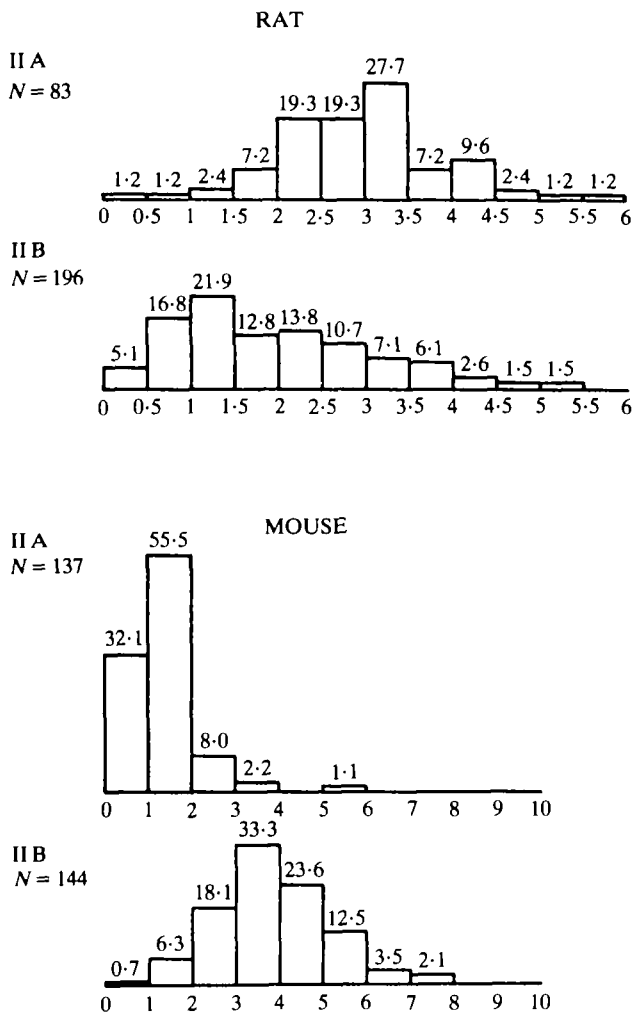

Fig. 5. Histograms of relative succinate dehydrogenase activity (as a percentage of total number of fibres studied) in histochemically typed IIA and IIB fibres of tibialis anterior in rat and mouse. Modified from Reichmann & Pette (1982).

dehydrogenase, a reference enzyme of aerobic oxidative metabolism, follows the pattern of myosin-based subgroups of fast-twitch fibres. As is evident from Fig. 5, a large fraction of IIA fibres of rat muscle displays high SDH activities, whereas the majority of IIA fibres in the mouse muscle is characterized by low activities. The majority of IIB fibres in the rat are low, whereas those in the mouse are high in SDH activity. Therefore, SDH is inversely distributed in IIA and IIB fibres of these rat and mouse muscles. It is obvious from Fig. 1 that no differences exist in tibialis anterior muscle of the human between the activity profiles of SDH in IIA and IIB fibres.

These results indicate that metabolic subpopulations of fast-twitch fibres do not coincide with subtypes defined by differences in myofibrillar actomyosin ATPase. On the other hand, it is evident that there exists a marked metabolic heterogeneity of both fast- and slow-twitch fibres. As judged from the results discussed so far, fast- and slow-twitch fibres represent metabolically distinct populations with partial overlaps of wide spectra of enzyme activities. It is probable that metabolic subgroups of the two main fibre types have escaped detection, because previous studies have more or less focused upon enzymes of main metabolic pathways. Metabolic subgroups might be more easily detected by studying enzymes involved in special metabolic functions.

METABOLIC HOMOGENEITY OF THE MOTOR UNIT

The hypothesis that muscle fibres belonging to the same motor unit are metabolically similar or identical has been suggested by Kugelberg & Edström (1968) from histochemical analyses. This notion was supported by microbiochemical enzyme activity determinations in fibres of identified motor units. Nemeth et al. (1981) studied malate dehydrogenase (MDH) which displays wide activity ranges both in fast- and slow-twitch fibre populations. However, it was found that activity levels of MDH were identical or very similar in the fibres of a given motor unit, but varied markedly between fibres of various motor units.

Further support for the metabolic homogeneity of the motor unit in mammalian muscles stems from recent microphotometric enzyme activity determinations in type-grouped fibres of reinnervated muscles (Vetter, Reichmann & Pette, 1984). Activity levels of four different enzymes were found to be similar in fibres of individual type-groups. These latter are believed to represent fibres of distinct motor units, which contrary to their normally random distribution, are assembled in close groups in reinnervated muscle.

Collectively, these observations support the idea that it is the specific neural input which is of primary importance in regulating the phenotype expression and consequently also the metabolic properties of a muscle fibre (Pette & Vrbová, 1985).

METABOLIC HETEROGENEITY, A MIRROR OF PATTERNS OF RECRUITMENT?

The motor unit assembly of muscle explains the existence of spectra of enzyme activities in muscle fibre populations. It is conceivable that metabolic differences

between motor units are due to differences in patterns of recruitment. This is in line with the notion that activity is a major factor in determining the phenotype of muscle fibres (Pette & Vrbová, 1985). In this context it is also understandable that heterogeneity of metabolic properties is less pronounced in immature muscle fibres of young animals. The adult pattern develops in response to increased activity (Reichmann & Pette, 1984a).

Variations in aerobic-oxidative capacity reflect differences in the ability to sustain contractile work. In agreement with histochemical findings (Edström & Kugelberg, 1968; Burke, Levine, Tsairis & Zajac, 1973), resistance to fatigue correlates with enzyme activities of terminal substrate oxidation. Fast-twitch fibres with high levels of malate dehydrogenase fatigue less than those with low levels of this enzyme (Nemeth *et al.* 1981). The enzyme activity pattern of energy metabolism is thus related to the amount and type of activity the motor unit is engaged in.

It is well established that changes in contractile activity as brought about by inactivity or endurance training, lead to marked alterations in the enzyme activity pattern of energy metabolism (for reviews see Holloszy & Booth, 1976; Saltin & Gollnick, 1983). Above all, the adaptability of metabolic properties to functional demands is convincingly shown by the rapid rearrangement of the enzyme activity pattern in response to chronic nerve stimulation (for review see Pette, 1984). As reflected by short half-lives of the enzymes of energy metabolism (Dölken & Pette, 1974; Pette & Dölken, 1975; Illg & Pette, 1979), muscle is capable of adapting its metabolic properties relatively fast to altered functional requirements.

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