"Slow" and "Fast" Muscle Fibers

ERNEST GUTMANN

Department of Physiology and Pathophysiology of the Neuromuscular System, Institute of Physiology, Czechoslovak Academy of Sciences, Prague

The great variety of structure and function of different muscles reflects apparently the process of adaptation to different functional demands, but it has remained a source of confusion, especially if an attempt is made to find a common principle of order for this variety. The terms "fast" and "slow" muscle fibers in mammals are used in reference to their faster or slower contraction times. Both these muscles, e.g., the fast M. Extensor digitorum (E.D.L.) and the slow M. soleus of the rat are "twitch" muscles, i.e., they react with propagated action potentials to nerve stimulation. Contrary to this, the slow-tonic muscle fibers of the frog respond with local non-propagated depolarizations, activating contractures (Tasaki and Mizutani, 1943; Kuffler and Gerard, 1947; Kuffler and Vaughan Williams, 1953). The normal responses of these "tonic" fibers in the body are long-lasting contractures, which they maintain in a graded fashion to depolarizing concentrations of acetylcholine (ACh) or potassium. In fact, localized responses to ACh in fast-twitch muscle fibers and slow long-lasting contractures in slow-tonic muscle fibers have already been described by Rieser and Richter (1925) and Sommerkamp (1928). Essential differences in contracture responses have been described in the fast (twitch) and slow (tonic) fibers of the frog, especially in their reactions to KCl solutions which initiate contractures by membrane depolarizations. A phasic contracture is evoked in fast fibers (Hodgkin and Horowicz, 1960), i.e., the fast fibers of the frog will relax relatively rapidly despite membrane depolarization, but the slow fibers of the frog show a sustained contracture during the whole period of reduced membrane potential (Kuffler, 1946; Fleckenstein, 1955).

Thus two distinct fiber types, i.e., fast (twitch) and slow (tonic) fibers do exist in frogs and toads and related differences have been described for the membrane potentials (Kuffler and Vaughan Williams, 1953; Kiessling, 1960), arrangement of muscle fibrils ("Fibrillen" or "Felderstruktur"), pattern of filaments and structure of the sarcoplasmatic reticulum (Krüger, 1952; Gray, 1958; Peachey, 1965), and type (focal or multiple) of innervation.

Krüger (1952) claimed that some mammalian muscles consist entirely of fibers with "Felderstruktur" and that the same distinction between muscle fibers with "Fibrillen" and "Felderstruktur" as in frog muscles could also be made in mammalian muscles. Mammalian muscle fibers with "Felderstruktur" showing only non-propagated junctional potentials in response to nerve stimulation have indeed been found in the extraocular muscles of the guinea-pig (Hess, 1961). However, in other mammalian muscles such a distinction has not been found. Moreover, no distinct structural differences could so far be detected between fast and slow mammalian muscle fibers.

Therefore, the question whether there are two fiber types or a whole spectrum of many different muscle fibers as regards structure, innervation, speed of contraction and type of electrical response in mammalian muscles is still unsettled (Huxley, 1964).

A study of the contracture responses in fast and slow mammalian muscle fibers especially during development should be rewarding. Contractures do in fact demonstrate the main features of the mechanisms of the process of excitation-contraction coupling, and the basic differences in the contracture responses to different agents in the two types of muscle fibers in the frog would suggest important modifications of this process (*see* Sandow, 1965). Are there any suggestions for such differentiation also in mammalian muscle fibers?

ACh CONTRACTURES IN E.D.L. AND SOLEUS MUSCLE OF THE RAT

Figure 1 shows that in both E.D.L. and soleus muscles of the rat (three days old), contractures to ACh can be produced. In figures 1 and 2 the contracture response and the tension developed during contracture respectively are expressed in percent of maximal tetanic tension output of the muscle. It can be seen that there is a considerably stronger contracture response in the soleus muscle than in the E.D.L. Moreover, contracture is observed at a threshold value of 10^{-7} in the soleus muscle, but at 7.10^{-7} in the E.D.L.

However, the fast E.D.L. loses the capacity to react with contractures to ACh about 20 to 25 days after birth of the animal, whereas the slow soleus muscle reacts to ACh, though to high concentrations only, with contractures at all stages of development. It is interesting to see that there are considerable differences in threshold and intensity of contracture response during the earliest stages of development that I have studied (Gutmann and Hanzlíková, in press). Very marked differences in contracture responses to ACh are, of course, known to exist between fast (twitch) and slow (tonic) muscle fibers of the frog. Similar qualitative differences exist between the fast Latissimus dorsi posterior (L.D.P.) and the slow Latissimus dorsi anterior (L.D.A.) of the chicken (Gutmann, Jirmanová and Vyklický, to be published). The L.D.P. does not react to ACh even at highest concentrations, whereas the L.D.A. reacts at relatively low concentrations of ACh with a sustained contracture.

CAFFEINE CONTRACTURES IN E.D.L. AND SOLEUS MUSCLE OF THE RAT

In the E.D.L. of animals 22 to 30 days old exposed to a 20 mM solution of caffeine, potentiation of twitch tension but no contracture is observed (Gutmann and Sandow, 1965). However, contracture responses to exposure of caffeine could be observed until the 18th to 22nd day after birth. No contracture was observed in this muscle of animals more than 22 days old. In contrast to the E.D.L., the soleus responds with contracture also in animals one month old. Thus the contracture response to caffeine is lost during ontogenesis in the fast E.D.L., but not in the soleus muscle which maintains sensitivity to this contracture-inducing drug. A similar contracture behavior is observed in the Latissimus dorsi of the chicken. The fast L.D.P. of adult animals shows no contracture, whereas the slow L.D.A. responds with a contracture to caffeine (Gutmann, Jirmanová, and Vyklický, 1966, to be published).

NERVOUS INFLUENCES AFFECTING CONTRACTURE BEHAVIOR OF MAMMALIAN MUSCLES

It is well known that during denervation the whole muscle fiber becomes sensitive to ACh (Ginetzinsky and Shamarina, 1942; Axelsson and Thesleff, 1958; Miledi, 1960; and others). Thus the denervated muscle shows the contracture behavior of muscle at early stages of development (Diamond and Miledi, 1962). A similar change in contracture behavior of denervated muscles is observed after exposure to caffeine. After denervation the E.D.L. of adult animals reacts to caffeine with contracture; it has thus gained properties of the slow muscle (Gutmann and Sandow, 1965). The student of differentiation between fast and slow muscle fibers will find many valuable clues from work comparing striated and smooth muscle, a line developed successfully, e.g., in respect to birefringence and other characteristics (Fischer, 1944). Slow muscle fibers and muscles during early stages of development resem-

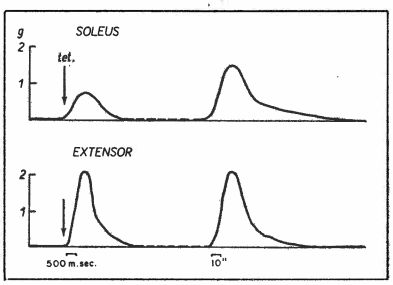

Fig. 1—Maximal isometric tetanic contraction (first curve) and contracture response to acetylcholine (second curve) added to the bathing solution at a concentration of 5.10^{-5} of M. soleus and M. extensor digitorum longus of three-day-old rats. Tetani were produced by "massive" direct stimulation in vitro by a 300-msec-long stimulus, the single stimuli being square shocks 1.0 msec in duration (*see* Sandow and Brust, 1958).

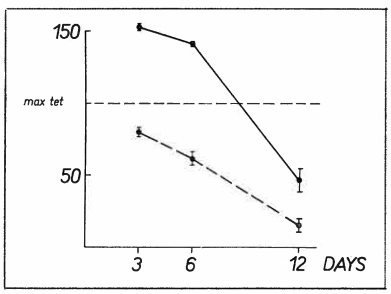

Fig. 2—Changes of contracture response of M. soleus (full line) and M. extensor digitorum longus (interrupted line) of rats 3, 6, and 12 days after birth. The contracture response is expressed in percent of the maximum isometric tetanus tension (= 100%), obtained by electrical stimulation in vitro.

ble in their reactions the smooth muscle. The comparative approach has and will certainly prove to be the most helpful concerning the problem of basic conceptions of contraction mechanisms (*see* Fischer, 1944). Hetero-innervation experiments were used to show the effect of an additional nerve supply on contracture behavior of the muscle (Gutmann and Hanzlíková, to be published). If the peroneal nerve is sutured into the soleus muscle (this is a hetero-innervation) and simultaneously the tibial nerve is crushed, hyperneurotization of the soleus muscle due to the additional supply of fast peroneal nerve fibers is achieved. The additional nerve supply affects the contracture behavior of the reinnervated soleus muscle, apparently by mediating fast nerve influences. In these experiments only the tibial nerve was crushed on the control side. Both muscles react with contracture to a solution of caffeine. Five weeks after reinnervation of the muscles, the tension developed by the contracture was 2.26 ± 0.26 g in the control muscles (reinnervated by the tibial nerve only) and 1.30 ± 0.24 g (10 animals) in the muscle reinnervated by tibial and hyperneurotized by peroneal nerve fibers. Thus the additional fast nerve influence had reduced the contracture response of the slow soleus muscle.

DIFFERENCES IN METABOLISM OF "FAST" AND "SLOW" MAMMALIAN MUSCLE FIBERS RELATED TO DIFFERENT CONTRACTURE BEHAVIOR

The differences in contracture behavior between fast and slow mammalian muscle fibers suggest that two basic groups of muscle fibers may exist, which may be somehow related to the differences of fast (twitch) and slow (tonic) muscle fibers of the frog. Are there indications of differences of metabolism between such basic groups of muscle fibers?

Our first consideration will, of course, be centered on the role of Ca^{++} ions, which have such an important role in the process of excitation-contraction coupling (*see* Sandow, 1965). It may suffice to point out that caffeine increases the capacity of the sarcoplasmatic reticulum to release Ca^{++} (*see* Sandow, 1965) and that ACh increases the inward movement of Ca^{++} following an increase in membrane permeability (Jenkinson and Nicholls, 1961). Moreover, the sarcoplasmatic reticulum, the structure which apparently mediates the process of excitation-contraction coupling, is relatively less developed in the slow (tonic) muscle fibers of the frog (*see* Page, 1965). In analogy, sensitization of the E.D.L. to caffeine contracture caused by denervation suggests alterations in the sarcoplasmatic reticulum and in its capacity to regulate the myoplasmic flux of Ca^{++} (Gutmann and Sandow, 1965).

Our next consideration concerns the well-known differences of energy metabolism of fast ("white") and slow ("red") muscles. In the former, anaerobic glycolysis, catalyzed by the enzymes of the Embden-Meyerhof chain, apparently plays the dominant role; in the latter, the oxidative processes catalyzed by enzymes of the citric acid cycle (the intramitochondrial enzymes dominate; *see* Pette, 1965). These differences are apparently related to adaptation to different functional demands (e.g., Needham, 1926; Yakovlev and Yakovleva, 1953) and are reflected in the differences of speed of contraction (Close, 1964).

However, slow (tonic) fibers of frog, toads, or chickens and slow mammalian muscle fibers alike are required for posture and maintenance of tension for long periods of time, and differences in protein metabolism of two basic types of muscle fibers related to "long-term regulations" might be expected. This is indeed the case.

Incorporation of radioactive amino acids into the proteins of the slow L.D.A. of chicken and of the soleus of rats is increased compared with that of the fast L.D.P. of chicken and the E.D.L. of rats (fig. 3). Also a higher level of ribonucleic acid content was found (mg RNA/100 mg of proteins) in the slow L.D.A. of the chicken, rectus abdominis of the frog and soleus of the rat compared with the fast L.D.P. of the chicken, sartorius of the frog and E.D.L. of the rat (Gutmann and Syrový, 1966, to be published). These are first indications of a higher turnover of proteins of slow muscles, but, of course, more data will be necessary to strengthen the assumption of a relation of speed of proteosynthesis and mechanisms concerned with maintenance of tension.

CONCLUSIONS

On the basis of the clear-cut differentiation used in fast (twitch)

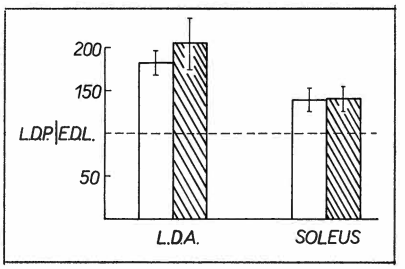

Fig. 3—Incorporation of radioactive S^{35} methionine into the proteins of the M. latissimus dorsalis anterior of the chicken and the M. soleus of rats (counts/min/mg of precipitated proteins) one hour after intraperitoneal injection of S^{35} methionine (200 μc/100 g of body weight). Specific activity is expressed in percent of activity measured in the M. latissimus dorsalis posterior of the chicken and the M. extensor digitorum longus of the rat (white columns). The levels of ribonucleic acid content (*see* Schneider, 1945) in L.D.A. of chicken and the M. soleus of the rat (γP/mg protein) are expressed in percent of the RNA content in the L.D.P. of the chicken and in the E.D.L. of the rat (black columns).

and slow (tonic) muscles of the frog, both the fast E.D.L. and the slow soleus muscle should be considered twitch muscles. However, they reveal a marked differential behavior in their contracture responses to ACh and caffeine. Moreover, all the slow muscles I have studied (i.e., the L.D.A. of the chicken, the rectus abdominis of the frog, and the soleus of the rat) show a higher rate of proteosynthesis. This may be related to the basic function of slow muscles concerned with long-lasting maintenance of tension, the extreme being, for example, the contracture responses observed in reaction to ACh. There may be a relation of rate of protein metabolism to the mobility of protein-bound Ca^{++} in the sarcoplasmatic reticulum. The differences in contracture behavior are apparent already three days after birth of the animals. All this may indicate a basic differentiation of two main groups of muscle fibers. Neural long-term influences operate in the development of this differentiation in contracture behavior of fast and slow muscle fibers. The mechanisms by which the nerve cell affects this behavior have still to be uncovered.

REFERENCES

AXELSSON, J. AND S. THESLEFF. Activation of the contractile mechanism in striated muscle. *Acta Physiol. Scand.* 44: 55–66, 1958.

CLOSE, R. Dynamic properties of fast and slow skeletal muscles of the rat during development. *J. Physiol.* 173: 74, 1964.

DIAMOND, J. AND R. MILEDI. A study of foetal and new-born rat muscle fibres. *J. Physiol.* 162: 393, 1962.

FISCHER, E. The birefringence of striated and smooth mammalian muscles. *J. Cellular Comp. Physiol.* 23: 113, 1944.

FISCHER, E. Vertebrate smooth muscle. *Physiol. Rev.* 24: 467–490, 1944.

FLECKENSTEIN, A. *Der Kalium-Natrium Austausch als Energieprincip in Muskel und Nerve.* Berlin, 1955.

GINETZINSKY, A. G. AND N. M. SHAMARINA. Tonomotornyj fenomen v denervirovanoj myšce. *Usp. Sovr. Biol.* 15: 283, 1942.

GRAY, E. G. Structures of fast and slow muscle fibres in the frog. *J. Anat.* 92: 559–562, 1958.

GUTMANN, E., I. JIRMANOVÁ, L. VYKLICKY. Contracture responses of the latissimus dorsi ant. and post. of the chicken, to be published.

GUTMANN, E. AND A. SANDOW. Caffeine-induced contracture and potentiation of contraction in normal and denervated rat muscle. *Life Sci.* 4: 1149, 1965.

GUTMANN, E. AND I. SYROVY. Protein metabolism in fast and slow muscle fibres, to be published.

GUTMANN, E. AND V. HANZLÍKOVÁ. Contracture responses of fast and slow mammalian muscles. *Physiol. Bohemoslov.*, in press.

HESS, A. The structure of slow and fast extrafusal muscle fibers in the extraocular muscles and their nerve endings in guinea pigs. *J. Cellular Comp. Physiol.* 58: 63, 1961.

HODGKIN, A. L. AND P. HOROWICZ. Potassium contractures in single muscle fibres. *J. Physiol.* 153: 386, 1960.

HUXLEY, A. F. Muscle. *Ann Rev. Physiol.* 26: 131–152, 1964.

JENKINSON, D. H. AND J. G. NICHOLLS. Contractures and permeability changes produced by acetylcholine in depolarized denervated muscle. *J. Physiol.* 159: 111–127, 1961.

KIESSLING, A. Die Abhängigkeit des Ruhepotentials der "tonischen" Skeletmuskelfasern des Frosches von den Ionengradienten. *Arch. Ges. Physiol.* (Pflüger) 270: 23–24, 1959.

KRÜGER, P. *Tetanus und Tonus der quergestreiften Skelettmuskeln der Wirbeltiere und des Menschen.* Leipzig, 1952.

KUFFLER, S. W. The relation of electrical potential changes to contracture in skeletal muscle. *J. Neurophysiol.* 9: 367–377, 1946.

KUFFLER, S. W. AND E. M. VAUGHAN WILLIAMS. Small-nerve junctional potentials. The distribution of small motor nerves to frog skeletal muscle, and the membrane characteristics of the fibres they innervate. *J. Physiol.* 121: 289–317, 1953.

KUFFLER, S. W. AND R. W. GERARD. The small-nerve motor system to skeletal muscle. *J. Neurophysiol.* 10: 383–394, 1947.

MILEDI, R. The acetylcholine sensitivity of frog muscle fibres after complete or partial denervation. *J. Physiol.* 151: 1–23, 1960.

MILEDI, R. Junctional and extrajunctional acetylcholin receptors in skeletal muscle fibres. *J. Physiol.* 151: 24–30, 1960.

PAGE, S. G. A comparison of the fine structures of frog slow and twitch muscle fibres. *J. Cell Biol.* 26: 477–497, 1965.

PEACHEY, L. D. Structure of the sarcoplasmic reticulum and T system of striated muscle. *Proc. Int. Union of Phys. Sci.* 4: 388, 1965.

PETTE, D. Plan und Muster in zellulären Stoffwechsel. *Naturwissenschaften* 52: 597, 1965.

NEEDHAM, D. M. Red and white muscle. *Physiol. Rev.* 6: 1, 1926.

RIESSER, O. AND F. RICHTER. Weitere Beitrage zur Kenntnis der Erregungs-contractur des Froschmuskels. *Arch. Ges. Physiol.* (Pflügers) 207: 287–301, 1925.

SANDOW, A. AND M. BRUST. Contractility of dystrophic mouse muscle. *Am. J. Physiol.* 194: 557–563, 1958.

SANDOW, A. Excitation-contraction coupling in skeletal muscle. *Pharmacol. Rev.* 17: 265, 1965.

SCHNEIDER, W. C. Extraction and estimation of desoxypentose nucleic acid and of pentose nucleic acid. *J. Biol. Chem.* 161: 293, 1945.

SOMMERKAMP, H. Das Substrat der Dauerverkürzung am Froschmuskel. *Arch. Exp. Pathol. Pharmacol.* (Naunyn-Schmiederberg) 128: 99–115, 1928.

TASAKI, I. AND K. MIZUTANI. *Jap. J. Med. Sci.* III. Biophysics 10: 237, 1943, cit. Peachey, L. D. Structure and function of slow striated muscle. In *Biophysics and Pharmacological Actions,* 1961.

YAKOVLEV, N. N. AND E. S. YAKOVLEVA. Basic biochemical and morphological changes of the muscle under the influence of systematic exercise. (In Russian: O zakonomernostyach biokhimicheskoi i morfologischeskoi perestroiki myshts pod vliyaniem ikh sistematicheskogo uprazhneniya). *Usp. Sovr. Biol.* 35: 134, 1953.