What Is Fatigue?

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Abstract/Résumé

Fatigue and potentiation are two forms of force modulation. A general definition of fatigue is "a circumstance where less than the anticipated contractile response is obtained." Fatigue is associated with depressed Ca^{2+} release and possibly decreased Ca^{2+} sensitivity. Potentiation results from increased Ca^{2+} sensitivity due to regulatory light chain phosphorylation. Muscle fatigue and potentiation can coexist, making it difficult to quantify these processes. With repetitive 10Hz stimulation, the developed tension first increases, then decreases. Is fatigue present when developed tension first begins to decrease or when it falls below the developed tension of the first response? Intermittent incompletely fused tetanic contractions for which peak developed tension first decreases, then increases, is another unusual example of fatigue. A third example is when twitch contractions following a tetanic contraction decrease to a level below the pretetanic twitch amplitude, indicating that fatigue may have been coexistent with posttetanic potentiation. These observations illustrate the complexity of detecting fatigue, based on the simple, but commonly accepted definition presented above. Care must be taken in interpreting "before vs. after" contractile responses. Even when the contraction amplitude is greater than the initial response, there is no guarantee that mechanisms associated with fatigue are not present.

La fatigue et la potentiation sont deux formes de modulation de la force pouvant respectivement la diminuer ou augmenter. La fatigue est généralement définie comme « une situation où moins de force est produite que prédite par la machine contractile ». La fatigue

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est associée à une moins grande libération de Ca^{2+} et, possiblement, à une diminution de la sensibilité au Ca^{2+}. La potentiation est associée à une augmentation de la sensibilité au Ca^{2+} par la phosphorylation de régulation des filaments minces. La fatigue et la potentiation peuvent coexister occasionnellement, ce qui rend difficile la caractérisation et la quantification des deux processus. Au cours d'une stimulation itérative de 10 Hz, la tension contractile augmente d'abord puis diminue. Parle-t-on de fatigue quand la tension commence à chuter ou quand la tension passe sous le niveau des premiers pics de tension ? Les contractions tétaniques intermittentes constituées de secousses sans fusion complète au cours desquelles la tension augmente avant de décliner est un autre exemple qui illustre la difficulté de caractériser la « fatigue ». Le troisième exemple de ce dilemme est illustré par la tension de secousse à la suite d'une stimulation tétanique diminuant à un niveau plus bas qu'avant la stimulation tétanique, ce qui indique que la fatigue coexistait probablement avec la potentiation posttétanique. Cet ensemble d'observations illustre bien la complexité de repérer une manifestation de la fatigue à la lumière de la simple définition précédente. Il faut donc analyser avec prudence les réponses contractiles des études avec un devis pré-post. Même en présence d'une augmentation de la tension à un niveau supérieur à la tension initiale, on ne peut pas affirmer que les mécanismes associés à la fatigue ne sont pas présents.

Introduction

What is fatigue? Everyone has a notion of what constitutes fatigue. We sense fatigue when we have exercised to the point that we feel that the task requires greater effort than it should. Fatigue can be of central origin (Gandevia et al., 1995; Taylor et al., 2000), in which case the muscles are capable of greater output than what the central nervous system is willing or able to request. In this case there is an unwillingness to activate the motor pathway to the extent expected, anticipated or required to perform the task. However, more commonly, and in many cases coincidentally, fatigue is of peripheral origin. In this case, the muscles are just incapable of responding in the same fashion as they were prior to the exercise that has elicited the fatigue. This paper will deal specifically with peripheral fatigue. In particular, this paper will present interactions among fatigue and factors that enhance the contractile response that typically occurs early in the period of repetitive contractions. Under these circumstances it is difficult to detect fatigue. However, if we can identify the circumstances when fatigue mechanisms are present, but masked by factors that potentiate the contractile response, then a better understanding of the mechanisms of fatigue can be obtained.

Definitions of Fatigue

Although fatigue is often defined as: "a reduced capacity for force development" (Bigland-Ritchie et al., 1986a; Fitts and Holloszy, 1976), this definition is inappropriate because it does not acknowledge the possibility of low-frequency fatigue. This definition permits a very discrete identification of the presence of fatigue, but requires a specific test to identify fatigue. To properly identify the presence of fatigue by this definition, it is necessary to maximally activate a muscle because that is the only way to quantify the "capacity" for force development. This may be difficult in vivo, but can be done easily during experiments in vitro with high frequency stimulation (usually in the presence of caffeine to assure maximal activation) or potassium depolarization. Low frequency fatigue is recognized to

occur when the contractile response to low frequency stimulation is diminished while at the same time, the response to high frequency stimulation is not affected (Jones, 1996; Jones et al., 1982). The capacity for force development is clearly not decreased during low frequency fatigue, yet this is a very real form of fatigue.

In this review, fatigue is defined as: "a response that is less than the expected or anticipated contractile response, for a given stimulation" (Asmussen, 1979; Bigland-Ritchie et al., 1986b). The advantage of this definition is that it is sensitive to the progressive changes in contractile performance during sustained exercise. Furthermore, this definition can be used to identify fatigue with any frequency of stimulation, therefore both low and high frequency fatigue can be identified. These advantages make this definition of fatigue the most universally accepted. The disadvantage of this definition is that some notion of the contractile response that is expected must be known. This is typically done by evaluating the contractile response with a specific stimulation pattern in a rested state. Subsequent comparison of the contractile response with this "control" condition permits the recognition of fatigue. There is a problem with this approach, in that repetitive submaximal activation of a muscle results initially in an enhanced response, potentiation, which is followed by a decreasing response. The next section of the paper provides a definition of potentiation, then the balance of this paper will deal with interactions of fatigue and potentiation, a circumstance where it is difficult to identify and/or quantify fatigue.

Definitions of Potentiation

Activity-dependent potentiation is a term which is used to refer collectively to any enhanced contractile response which results from prior contractile activity. There are two primary forms of activity-dependent potentiation: staircase and posttetanic potentiation. Staircase is the progressive increase in contractile response that is observed during low-frequency stimulation (see Figure 1). This form of potentiation

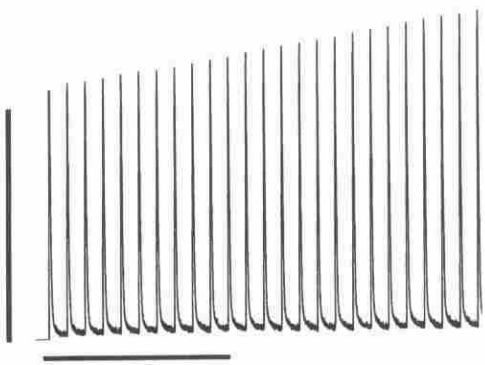

Figure 1. Low frequency stimulation results in a progressive enhancement of developed tension over the first several seconds. Here, stimulation of the whole gastrocnemius muscle of the rat in situ at 5 Hz for 7 s is illustrated. The increase in developed tension is apparent with the second stimulation. Muscle temperature was regulated at 37 °C and stimulation was with square wave pulses, 50 μs duration via the sciatic nerve.

is primarily seen in fast-twitch mammalian muscle (Moore and Stull, 1984). Posttetanic potentiation is the enhanced twitch response that follows a tetanic contraction (see Figure 2). A third term associated with potentiation, postactivation potentiation, describes the enhanced twitch response following a voluntary contraction. Typically, these three terms are used to describe the isometric twitch response under these specific conditions. However, enhanced power (Grange et al., 1998) has been observed during and following repetitive stimulation, and enhanced contractile response (force, shortening and velocity of shortening) during incompletely fused tetanic contractions has also been reported (see Figure 3). It is proposed here that the term activity-dependent potentiation be used to refer to any condition of enhanced contractile response that can be attributed to prior contractile activity.

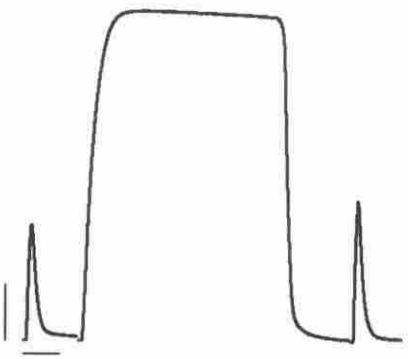

Figure 2. A twitch contraction prior to and after a tetanic contraction (200 Hz for 500 ms) illustrates the presence of posttetanic potentiation in a rat gastrocnemius muscle. The (vertical) force calibration bar represents 1N force for the twitch contractions and 2N force for the tetanic contraction. The horizontal calibration bar represents100 ms. Muscle temperature was regulated at 37 °C and stimulation was with square wave pulses, 50 μs duration via the sciatic nerve.

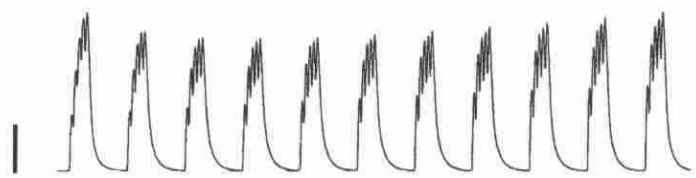

Figure 3. Intermittent submaximal isometric contractions of the rat medial gastrocnemius muscle resulting from trains of 5 pulses at 60 Hz every 0.5 s. This stimulation results in incompletely fused tetanic contractions. There is a down then up staircase, that results in enhancement of the peak developed tension to values greater than initial peak developed tension after several seconds. (source: MacIntosh and Willis, (2000) with permission). Muscle temperature was regulated at 37 °C and stimulation was with square wave pulses, 50 μs duration via the sciatic nerve.

Mechanisms of Contractile Response Modulation

It is clear from the above discussion that the contractile response can be modulated in either a positive or a negative direction as a result of prior contractile activity. Positive modulation is referred to as potentiation and negative modulation is referred to as fatigue. If the mechanisms for these two processes can coexist, then measurement of the magnitude of potentiation and detection of fatigue will be compromised. Since both fatigue and potentiation can result from contractile activity, it seems inevitable that coexistence will occur (Rankin et al., 1988; Green and Jones, 1989; Rassier and MacIntosh, 2000). Although it is recognized that such modulation can refer to dynamic (MacIntosh and Bryan, 2000) as well as isometric contractions, subsequent consideration in this paper will be given only to isometric contractions. The next step towards understanding the interactions of fatigue and potentiation is to consider the mechanisms associated with each of these processes.

FATIGUE

Failure in any of the several steps in excitation-contraction coupling can result in fatigue (for reviews, see Allen et al., 1995 and Karlsson, 1979). Ultimately, however, the mechanism of fatigue can be related to the force-Ca^{2+} relation (see Figure 4). Fatigue can result from either lower free Ca^{2+} concentration associated with a given stimulation (Allen et al., 1995), or from decreased sensitivity of the contractile proteins at a given Ca^{2+} concentration (Cooke et al., 1988). Although much has been made of the possible contribution of reduced sensitivity to Ca^{2+} due to accumulation of inorganic phosphate or hydrogen ions, recent evidence has indicated that at close to physiological temperatures, this mechanism plays a minor or negligible role (Pate et al., 1995; Westerblad et al., 1997). The primary mechanism of fatigue,

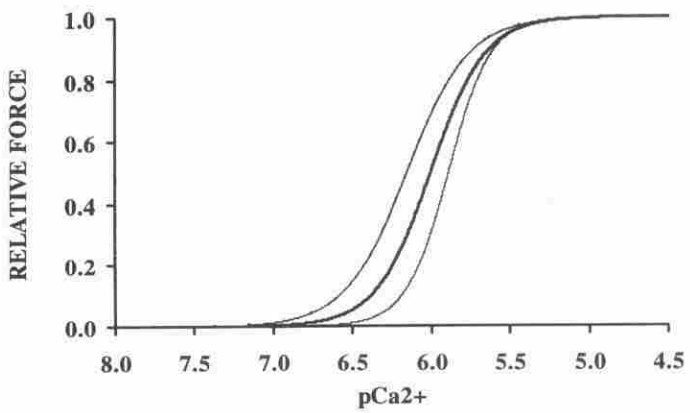

Figure 4. A hypothetical force-pCa^{2+} relation is shown. The thick line in the middle represents a muscle with no recent prior stimulation. The thinner lines represent situations with increased (shifted to the left), or decreased (shifted to the right) calcium sensitivity. Presumably potentiation will cause a shift to the left, and fatigue may cause a shift to the right. Calcium sensitivity is increased by RLC phosphorylation.

particularly low frequency fatigue, is apparently attenuated Ca^{2+} transients. Decreased free Ca^{2+} concentration under these circumstances could relate to less Ca^{2+} release, or faster uptake of Ca^{2+} (an abbreviated transient). Essentially in either case, there is less Ca^{2+} that becomes bound to troponin, and therefore less force will be developed. Considering the known mechanisms of force production, another possible cause of fatigue is a reduced force per cross-bridge. There is evidence that this mechanism plays a minor role in some instances (Edman and Lou, 1990).

It should be pointed out that the traditional force-Ca^{2+} relationship, as depicted in Figure 4 is obtained with steady state conditions in a skinned fiber preparation. Interpretation of these mechanisms for intact muscle fibers requires a liberal interpretation of this relationship, because the Ca^{2+} transient occurs too quickly for a steady state to be established (Sun, Lou, and Edman, 1996).

There are several possible mechanisms that could lead to decreased Ca^{2+} release from the sarcoplasmic reticulum. These include impaired neuromuscular transmission, attenuated membrane action potential, impaired voltage sensor, disrupted communication between the dihydropyridine receptor and the ryanodine receptor, impaired sarcoplasmic reticulum Ca^{2+}-channel opening, and decreased free Ca^{2+} concentration in the terminal cisternae. There are also several possible mechanisms for decreased free Ca^{2+} concentration in the terminal cisternae including: displacement of Ca^{2+} to mitochondria, or longitudinal sarcoplasmic reticulum, loss of Ca^{2+} from the cells, and precipitation of Ca^{2+} with inorganic phosphate within the sarcoplasmic reticulum. It should be considered that several of these mechanisms could coexist, contributing jointly to the decreased Ca^{2+} release.

ACTIVITY-DEPENDENT POTENTIATION

Activity-dependent potentiation could theoretically occur as a result of either an increase in Ca^{2+} sensitivity or an increase in Ca^{2+} release (and subsequent Ca^{2+} binding to troponin). However, potentiation is thought to occur primarily as a result of phosphorylation of the regulatory light chains of myosin (Sweeney et al., 1993; Grange et al., 1993), a process mediated by myosin light chain kinase. This enzyme, when activated by a Ca^{2+}-calmodulin complex, will increase the phosphate content of the regulatory light chains of myosin. With each activation, there is a Ca^{2+} transient, and subsequent activation of myosin light chain kinase. Therefore when there is a series of activations of a muscle, the phosphate content of the regulatory light chains will increase. It is thought that the added phosphate with its associated negative charge results in swinging of the cross-bridge away from the thick filament backbone, bringing the globular head of the cross-bridge in close approximation to the thin filaments (Levine et al., 1996). Myosin regulatory light chain phosphorylation therefore increases the probability for cross-bridge interaction, enhancing the rate at which cross-bridges engage. This results in an increase in Ca^{2+} sensitivity (see Figure 4).

INTERACTIONS OF FATIGUE AND ACTIVITY-DEPENDENT POTENTIATION

Three examples of the co-existence of fatigue and activity-dependent potentiation will be presented. The first of these three examples occurs during repetitive 10 Hz stimulation. The second relates to an intriguing down then up "staircase" during intermittent incompletely fused tetanic contractions. The third example of

co-existence of fatigue and activity-dependent potentiation occurs following a tetanic contraction. The experiments represented by these three examples all used, the *in situ* rat gastrocnemius muscle preparation. Stimulation was in all cases, indirect (via the sciatic nerve), and the muscle was kept at 37 °C with blood flow intact. In each case described below, the definition of fatigue: "less than the anticipated contractile response for a given stimulation" will be used. In some cases, it becomes difficult to determine what the anticipated response should be.

STAIRCASE AT 10 HZ

When the rat gastrocnemius muscle is stimulated at 10 Hz, it reaches a peak of staircase in about 10 s, then isometric developed tension begins to decrease (MacIntosh and Kupsh, 1987; MacIntosh et al., 1994). The enhanced contractile response is referred to as staircase (see Figure 1). The decrease may be related to fatigue. The question is: when does fatigue begin? If the anticipated response to which we are comparing subsequent responses is a twitch obtained prior to the 10 Hz stimulation, then fatigue begins when the developed tension during the 10 Hz stimulation falls below the developed tension of the first contraction in these responses. This occurs after about 20 s of this stimulation (see Figure 5). If the decrease in developed tension from 10 s to 20 s is the result of dissipation of the potentiating mechanism, then this conclusion would probably be correct. To identify the presence of fatigue it is necessary to have knowledge of the anticipated contractile response. If it could be expected that developed tension would continue to increase after 10 s in the absence of fatigue, then fatigue is first evident when the developed tension does not increase in sequential contractions.

To determine if we might otherwise expect developed tension to continue to increase after 10 s, it would be worth looking at the progression of change in regulatory light chain phosphorylation during the 10 Hz stimulation. It is known

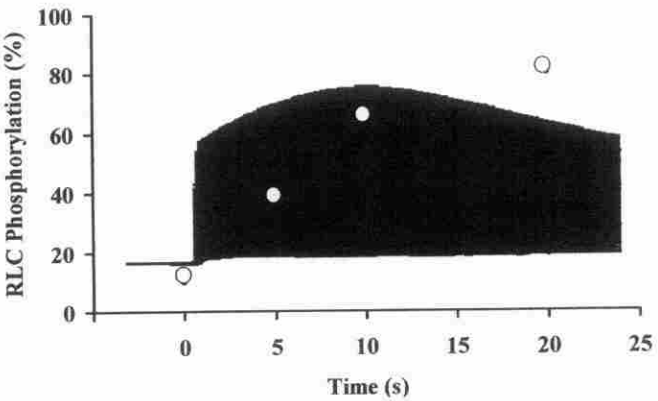

Figure 5. A pen-chart tracing (solid black) of the contractile response to repetitive 10Hz stimulation is shown. Developed tension reaches a peak after about 10 s, then begins to decline. Corresponding values for RLC phosphorylation are shown with circles. Source: MacIntosh and Kupsh (1987) and MacIntosh et al. (1994). Muscle temperature was regulated at 37 °C and stimulation was with square wave pulses, 50 μs duration via the sciatic nerve.

that light chain phosphorylation increases during the first 20 s of 10 Hz stimulation (see Figure 5). If potentiation is due to regulatory light chain phosphorylation, then some factor (fatigue) is present from 10 to 20 s, that prevents activity-dependent potentiation from being further expressed during this time. Therefore, fatigue is present from at least 10 s on. The question of whether or not the mechanism of fatigue is present prior to 10 s cannot be addressed with current knowledge, but should be considered a possibility. If we knew how much potentiation could be expected for a given level of phosphorylation of the regulatory light chains, then we could identify the presence of fatigue more precisely.

INTERMITTENT INCOMPLETELY FUSED TETANIC CONTRACTIONS

It was pointed out in the definition of activity-dependent potentiation that the contractile response of repeated submaximal incompletely fused tetanic contractions has a form of staircase associated with it. During intermittent stimulation with 5 pulses per train at 50 or 60 Hz, and 2 trains per s, peak developed tension is greater after 7 s than in the initial contraction (MacIntosh and Willis, 2000), as is evident in Figure 3. An interesting feature of this form of activity-dependent potentiation is that it is associated with a down then up response. Should we refer to the initial decrease in the peak response as fatigue? To answer this question, we have to consider what contractile response should be anticipated. If the contractile response is less than that which is anticipated, then we have fatigue.

A clue into the underlying mechanism associated with this sequence of stimulation is obtained by looking at the first response of each contraction. The rise and fall of tension which is attributed to the first pulse of each train is similar to a twitch contraction that is interrupted by a subsequent activation before complete relaxation can be achieved. Careful examination of the first 4 contractions in this sequence (Figure 6) reveals that the first response rises progressively in sequential

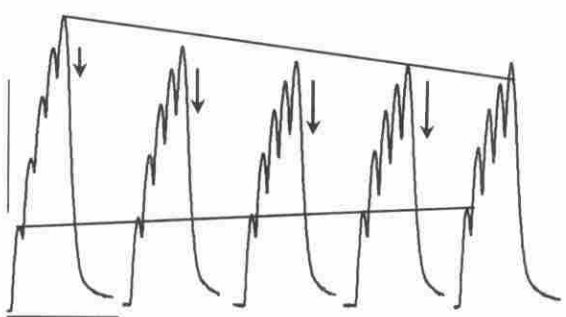

Figure 6. The first four contractions of a rat medial gastrocnemius muscle during intermittent stimulation with trains of pulses, 60Hz for 5 pulses, 2 per s (i.e., from Figure 3). The upper horizontal line (downward sloping) shows the decreasing peak developed tension. The lower horizontal line (upward sloping) shows the rising first response. A vertical arrow has been added to each contraction to show the magnitude of relaxation between the contractile response to the fourth stimulating pulse, and that due to the fifth stimulating pulse. Adapted from MacIntosh and Willis (2000). Muscle temperature was regulated at 37 °C and stimulation was with square wave pulses, 50 μs duration via the sciatic nerve.

contractions. This can be explained by the mechanism of potentiation described previously. Repetitive stimulation should result in activation of myosin light chain kinase (Blumenthal and Stull, 1980), and subsequent phosphorylation of the regulatory light chains (Grange et al., 1993). We associate increasing regulatory light chain phosphorylation with increasing Ca^{2+} sensitivity (Persechini et al., 1985; Sweeney and Stull, 1990). Therefore, it can be concluded that the enhanced first response is due to improved Ca^{2+} sensitivity. While the first response is rising, the peak tension is decreasing. If light chain phosphorylation is increasing from the first to the fourth contraction, then why does the peak developed tension continue to decrease over this time?

Once again, a close look at the contractile responses during the first four contractions reveals a potential mechanism for the decreasing peak response. It is clear that during sequential contractions, the amount of relaxation between activating pulses is increasing from one contraction to the next during the first four contractions (vertical arrows in Figure 6). A faster rate of relaxation might be due to either of two mechanisms: a faster dissociation of Ca^{2+} from troponin, or an accelerated dissociation of cross-bridges. According to our discussion of the force-Ca^{2+} relation above, an accelerated removal of Ca^{2+} from the sarcoplasm would result in less Ca^{2+} being available to bind troponin. This mechanism would result in less developed tension than would otherwise be expected. Altered cross-bridge kinetics would also result in an apparent decrease in Ca^{2+} sensitivity. Accelerated cross-bridge dissociation would result in fewer cross-bridges in the force-generating state during steady-state contraction, and therefore lower force development. It is interesting to point out that this unique form of fatigue is evident after just five stimulating pulses. It seems highly unlikely that metabolic limitations are involved in this response.

Accelerated relaxation is a characteristic feature associated with repetitive stimulation (MacIntosh, 1991). Figure 7 illustrates the changes in relaxation seen during the first few seconds of 10 Hz stimulation. In this figure, relaxation has been measured as a half-relaxation time, measured either from the peak of the contraction to half of the developed tension, or from half of the developed tension to 25% of the developed tension. A similar pattern of decrease followed by an increase in relaxation time is evident regardless of which portion of the relaxation curve of the twitch is measured. However, the relative magnitudes are different. The initial decrease is greater when measured late on the twitch, and the subsequent slowing of relaxation is greater when measured early on the twitch. If it is assumed that the Ca^{2+} transient is over relatively early in the twitch, then the fact that accelerated relaxation is more evident relatively late in the twitch would indicate that it is likely due to changes in cross-bridge kinetics, rather than changes in Ca^{2+} handling. The later increase in half-relaxation time may more likely be related to Ca^{2+} handling (slowed reuptake) since it is more evident when relaxation is measured early in relaxation. Accelerated dissociation of cross-bridges would equate to decreased Ca^{2+} sensitivity, a mechanism of fatigue.

A rather unique aspect of this fatigue is that it is present when stimulation frequency during these trains is 50–60 Hz, but is not evident at frequencies below or above this range (see Figure 8). It is not entirely clear why this range of frequencies is more sensitive to this form of fatigue, but it may be that higher stimulation frequencies mask the effect of accelerated relaxation because the next stimulus

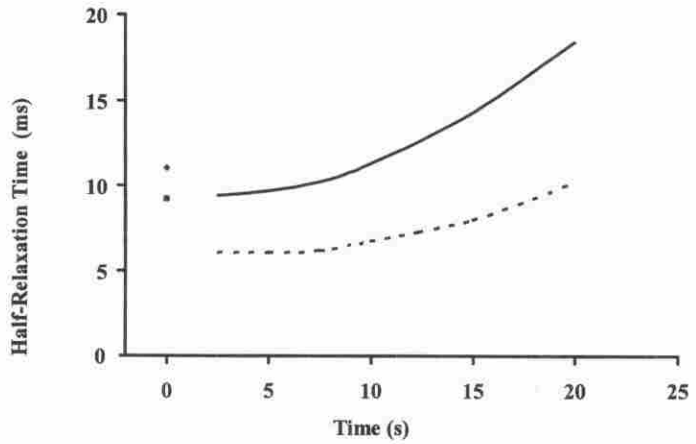

Figure 7. Half-relaxation times are shown for twitch contractions of the rat gastrocnemius muscle during 10 Hz stimulation. The upper line represents the change in half-relaxation time measured from the peak of the contraction to half of the developed tension. The lower (dashed) line illustrates the time-course of change in half-relaxation time measured from half of the developed tension to one quarter of the developed tension on the declining side of the twitch. The two patterns are very similar, but the relative initial decrease in + time is greater when measured later in the twitch, and the later increase is more evident when measured earlier in the twitch (adapted from MacIntosh et al., 1994). Muscle temperature was regulated at 37 °C and stimulation was with square wave pulses, 50 μs duration via the sciatic nerve.

arrives before much relaxation can occur. At lower frequencies, there is near complete relaxation between sequential activating pulses, so the impact of accelerated relaxation on the summation of force is diminished.

POSTTETANIC DEPRESSION OF CONTRACTILE RESPONSE

In the time immediately following a tetanic contraction, there is an enhanced contractile response that is referred to as posttetanic potentiation. How do we know that this response is not attenuated by fatiguing mechanisms? If the twitch response is followed for some time after the tetanic contraction, then in some cases fatigue becomes evident (see Figure 9). If the twitch response falls below the twitch amplitude that was evident prior to the tetanic contraction, then fatigue is present. Assuming that the test twitches during the period of posttetanic potentiation did not induce the fatigue, then apparently fatigue was present from some time during the tetanic contraction. In fact there may have been some recovery from whatever fatigue had been present at the end of the tetanic contraction by the time the potentiation dissipated and the fatigue became apparent. If it is assumed that there is a linear recovery from fatigue, that is initiated immediately after the tetanic contraction, then the apparent effect of fatigue can be quantified. From 12 s to 15 s, relative tension increases from 0.87 to 0.91, or 0.013 per s. Therefore at t = 0 s relative tension would have been depressed by 0.2. The magnitude of potentiation should have been 0.91 above the pretetanic twitch amplitude (i.e., 1.91). By this reasoning,

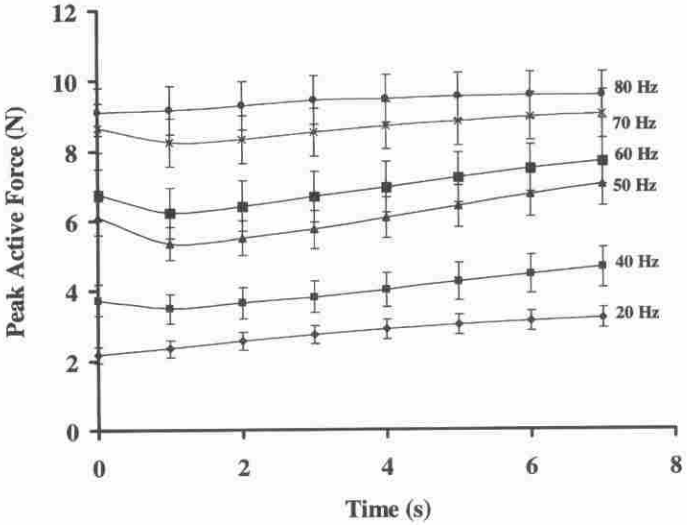

Figure 8. Mean values (±SEM) for developed tension during intermittent tetanic contractions of the medial gastrocnemius muscle in situ (2 per s) elicited with trains containing 5 pulses. The frequency of stimulation ranged from 20 Hz to 80 Hz. There is an apparent enhancement of developed tension after seven seconds in all cases up to and including 70 Hz stimulation. When stimulation was 50 Hz or 60 Hz, there was a down then up staircase. Source: MacIntosh and Willis (2000), with permission. Muscle temperature was regulated at 37 °C and stimulation was with square wave pulses, 50 μs duration via the sciatic nerve.

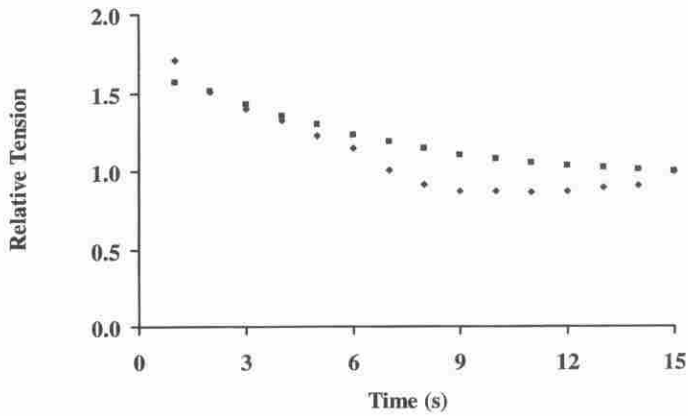

Figure 9. Examples of the amplitude of twitch contractions of the rat gastrocnemius muscle obtained after tetanic contractions (200 Hz for 1s) are shown. Developed tension is expressed relative to a control twitch. Developed tension is clearly enhanced immediately after the tetanic contraction, and decreases in one case to a value below the amplitude of a control twitch. Muscle temperature was regulated at 37 °C and stimulation was with square wave pulses, 50 μs duration via the sciatic nerve.

the enhanced twitch response after the tetanic contraction was apparently of lower amplitude than should have been expected. Fatigue was present even though twitch developed tension was greater than that prior to the tetanic contraction.

How Do We Detect Fatigue?

Clearly, there are circumstances when fatigue coexists with potentiation, resulting in a contractile response that is greater than that of a rested contraction, but less than what could be expected if fatigue was not present. There is compelling evidence to suggest that several mechanisms that contribute to modulation of the contractile response can be present at the same time. This situation makes it difficult to detect fatigue, although there are some indications that make it less or more clear.

CLEARLY FATIGUED

There are circumstances where the contractile response is less than the corresponding response prior to the exercise or activity. Under these circumstances, fatigue is present and easy to detect as a decreased contractile response for a given stimulation. However, quantifying fatigue may still be complicated by the continued presence of mechanisms that potentiate the contractile response. In other words, if potentiating mechanisms were not present, a greater magnitude of fatigue would be evident.

HIDDEN FATIGUE

Fatigue is less evident when the mechanisms that tend to decrease the contractile response are coexistent with mechanisms that tend to enhance the contractile response and the contractile response is greater than the initial response. This situation should none-the-less be recognized as fatigue, although outright evidence of fatigue is lacking. To detect such fatigue, it is necessary to very carefully evaluate what the anticipated response should be, or demonstrate the presence of mechanisms we associate with fatigue.

In order to detect fatigue when it is masked by potentiation, it is necessary to look for evidence of decreased Ca^{2+} transients, or decreased Ca^{2+} sensitivity which may be due to altered cross-bridge kinetics, or altered binding of Ca^{2+} to troponin. There are certainly going to be circumstances when it is difficult to confirm the presence of fatigue, and it will be difficult to quantify fatigue or potentiation when the other is present.

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