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Exercise-Induced Muscle Damage and Potential Mechanisms for the Repeated Bout Effect

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Abstract

Unfamiliar, predominantly eccentric exercise, frequently results in muscle damage. A repeated bout of similar eccentric exercise results in less damage and is referred to as the 'repeated bout effect'. Despite numerous studies that have clearly demonstrated the repeated bout effect, there is little consensus as to the actual mechanism. In general, the adaptation has been attributed to neural, connective tissue or cellular adaptations. Other possible mechanisms include, adaptation in excitation-contraction coupling or adaptation in the inflammatory response.

The 'neural theory' predicts that the initial damage is a result of high stress on

a relatively small number of active fast-twitch fibres. For the repeated bout, an increase in motor unit activation and/or a shift to slow-twitch fibre activation distributes the contractile stress over a larger number of active fibres. Although eccentric training results in marked increases in motor unit activation, specific adaptations to a single bout of eccentric exercise have not been examined.

The 'connective tissue theory' predicts that muscle damage occurs when the noncontractile connective tissue elements are disrupted and myofibrillar integrity is lost. Indirect evidence suggests that remodelling of the intermediate filaments and/or increased intramuscular connective tissue are responsible for the repeated bout effect.

The 'cellular theory' predicts that muscle damage is the result of irreversible sarcomere strain during eccentric contractions. Sarcomere lengths are thought to be highly non-uniform during eccentric contractions, with some sarcomeres stretched beyond myofilament overlap. Loss of contractile integrity results in sarcomere strain and is seen as the initial stage of damage. Some data suggest that an increase in the number of sarcomeres connected in series, following an initial bout, reduces sarcomere strain during a repeated bout and limits the subsequent damage.

It is unlikely that one theory can explain all of the various observations of the repeated bout effect found in the literature. That the phenomenon occurs in electrically stimulated contractions in an animal model precludes an exclusive neural adaptation. Connective tissue and cellular adaptations are unlikely explanations when the repeated bout effect is demonstrated prior to full recovery, and when the fact that the initial bout does not have to cause appreciable damage in order to provide a protective effect is considered. It is possible that the repeated bout effect occurs through the interaction of various neural, connective tissue and cellular factors that are dependent on the particulars of the eccentric exercise bout and the specific muscle groups involved.

1. Evidence for the Repeated Bout Effect

Unfamiliar eccentric exercise frequently results in muscle damage, the symptoms of which include strength loss, pain, muscle tenderness and elevated creatine kinase activity. Following recovery, a repeated bout of the same exercise results in minimal symptoms of muscle damage and has been referred to as the 'repeated bout effect'.[1] This protective effect of prior exercise was first indicated by Highman and Altland[2] and specifically attributed to eccentric contractions in later work.[3] The repeated bout effect has subsequently been demonstrated in humans and in animal models, with various types of activities using different muscle groups (table I).[1,3-20] Many theories have been proposed to explain the repeated bout effect but a specific mechanism has not been identified. In general, 3 categories of hypotheses have been proposed to explain this phenomenon which are neural, mechanical and cellular in origin. Other theories include adaptations in excitation-contraction (E-C) coupling[21,22] and reduced inflammatory response.[17]

2. Neural Theory

2.1 Neural Control of Eccentric Contractions

The terms 'eccentric contraction', 'pliometric contraction', 'lengthening contraction', 'eccentric activation' and 'eccentric action' have been used synonymously to describe what happens when the force generated by a muscle is less than the opposing load. In agreement with the position adopted by the American College of Sports Medicine,[23]

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Table I. Studies demonstrating the repeated bout effect

Population	Muscle group	Exercise mode	Delay between bouts	Proposed mechanism	Reference
12 men	Elbow flexors	Isotonic at 80% MVC	3 and 6 days	Neural adaptation	1
84 rats	Soleus, vastus intermedius, triceps medialis	Downhill running, level running	3-8 days	Strengthening of muscle tissue	3
11 women, 5 men	Lower extremity muscles	Downhill walking	1-8 weeks	No mechanism discussed	4
18 women, 6 men	Knee extensors	Maximal isokinetic	3 weeks	Improved ability to repair initial injury	5
11 women, 11 men	Lower extremity muscles	Downhill running	3, 6 or 9 weeks	Removal of weak fibres	6
8 women	Elbow flexors	Maximal isotonic	2 weeks	Connective tissue adaptation or removal of weak fibres or strengthening of cell membrane	7
20 women	Elbow flexors	Maximal isotonic	5 or 14 days	Strengthening of connective tissue or cell membrane	8
10 men	Quadriceps	Downhill running following maximal isokinetic quadriceps exercise	2 weeks	No mechanism discussed	9
9 women	Quadriceps	Cycling	8 weeks' training	Serial addition of sarcomeres or intermediate filament remodelling	10
15 men	Quadriceps	Cycling	4 and 8 weeks' training	Reorganisation of intermediate filament	11
24 men	Quadriceps	Isotonic at ≤85% MVC	3 weeks	Neural adaptations	12
67 rats	Vastus intermedius	Downhill running	1-3 weeks	Serial addition of sarcomeres	13
22 men	Quadriceps	Maximal isotonic	4 and 13 days	Removal of weak fibres or connective tissue adaptation or neural adaptation	14
5 women, 3 men	Elbow flexors	Maximal isotonic	2 and 4 weeks	Connective tissue adaptation and/or removal of weak fibres	15
9 men	Lower extremity muscles	Downhill running	4 days	Increased tissue strength or neural adaptation	16
10 men	Elbow flexors	Maximal isotonic	3 weeks	Decreased inflammatory response	17
Mice[a]	Tibialis anterior	Supramaximal nerve stimulation	10, 21, 84 or 166 days	Excludes possibility of neural adaptation	18
3 women, 3 men	Lower extremity muscles	Downhill running	2 weeks	Neural adaptation	19
4 women, 3 men	Lower extremity muscles	Downhill running	2 weeks	No mechanism discussed	20

a number not stated.

MVC = maximal voluntary contraction.

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the term 'eccentric contraction' is used in this review.

Exercise-induced muscle damage is associated with exercise involving a predominance of eccentric contractions.[24-26] Specific neural control of eccentric contractions has been implicated in the initiation of muscle damage[27] and the repeated bout effect.[1,12,14,16] It is well established that for a given force production, less motor unit activation is required for eccentric compared with concentric contractions.[27-31] Bigland and Lippold[29] showed surface electromyograph (EMG) amplitudes for eccentric contractions of the plantar flexors to be approximately 50% of concentric contractions at similar force levels. Similar results have been demonstrated in the elbow flexors (eccentric EMG 56% of concentric)[31] and the knee extensors (eccentric EMG 49% of concentric).[30] Moritani et al.[27] proposed that muscle damage was a result of high stress on a small number of active fibres during repeated eccentric contractions.

In addition to less motor unit activation, some authors have suggested that high threshold motor units are selectively recruited during submaximal eccentric contractions.[32-34] Nardone et al.[33] identified motor units according to their recruitment threshold during ramp isometric contractions of the plantar flexors. Individuals then performed reciprocal low intensity [<20% maximal voluntary contraction (MVC)] eccentric and concentric contractions. Interestingly, some motor units were activated during the eccentric portion that had been silent during both the concentric portion and the ramp isometric contractions. The amplitude of the action potentials from these units were consistent with high threshold motor units. Additionally, the soleus (predominantly slow twitch) appeared to be inhibited during the eccentric contractions with a corresponding increase in gastrocnemius (predominantly fast twitch) activation. These observations were taken to represent selective recruitment of high threshold motor units with a predominance of fast twitch fibres for submaximal eccentric contractions.

In contrast with the findings of Nardone and Schieppati[34] and Nardone et al.[33] analysis of the frequency content of the surface EMG signal during submaximal eccentric contractions of the elbow flexors[27,31] or maximal eccentric contractions of the quadriceps[35] failed to demonstrate evidence for selective recruitment of high threshold motor units. In fact, Nakazawa et al.[36] provided evidence of de-recruitment of high threshold motor units during submaximal eccentric contractions of the elbow flexors. However, as suggested by Potvin,[31] similar frequencies at lower activation levels may indicate preferential high threshold motor unit recruitment during eccentric contractions.

Selective recruitment of high threshold motor units would be expected to increase the rate of fatigue. However, maximum eccentric contractions have been shown to be extremely fatigue resistant despite high force production.[35,37] Hortobágyi et al.[37] demonstrated force decrements of 41 and 32% following maximal isometric and concentric contractions of the plantar flexors contrasted with no change in force following eccentric contractions. Similarly Tesch et al.[35] demonstrated 34 to 47% fatigue following maximal concentric contractions of the quadriceps with no fatigue following the same number of maximal eccentric contractions. Concentric fatigue was associated with a decrease in the mean power frequency (MPF) of the EMG signal with no change in MPF during eccentric contractions. These results are consistent with fatigue in fast fatigable motor units with concentric contractions contrasting with sustained function of fast fatigable motor units during eccentric contractions.

Although it was suggested that the mechanism of fatigue is fundamentally different for eccentric compared with concentric contractions,[35] specific mechanisms were not discussed. Lower energy demand may explain the fatigue resistance for eccentric contractions. Komi et al.[30] demonstrated greater mechanical efficiency (ratio of output to input energy) for eccentric (85%) compared with concentric contractions (19%) of the knee extensors.

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While the possibility of selective recruitment of high threshold motor units remains uncertain, it appears that fast twitch fibres are more susceptible to damage during eccentric exercise.[11,38-40] Fridén et al.[38] found myofibrillar disruption to be 3 times more prevalent in fast compared with slow twitch fibres 3 days after eccentric bicycle ergometer exercise. It is possible that selective recruitment of a small number of high threshold motor units places excessive stress on fast twitch fibres leading ultimately to damage of these fibres. A neural recruitment pattern combining less motor unit activation, selective fast twitch fibre recruitment and fatigue resistance may predispose the muscle to injury.

2.2 Potential Neural Adaptations

Several authors have discussed the possibility that there is a change in motor unit recruitment during the repeated bout, which limits the extent of damage.[1,12,14,16] Specifically, Golden and Dudley[12] suggested that less motor unit activation associated with eccentric contractions 'may provide the opportunity to 'learn' more efficient recruitment' for a repeated bout. Accordingly, Pierrynowski et al.[17] suggested that 'increased synchrony of motor unit firing' may reduce myofibrillar stresses during a repeated bout. Similarly, Nosaka and Clarkson[1] suggested that the neural adaptation would 'better distribute the workload among fibres'.

Several studies point to the potential for neural adaptation. In strength training studies, greater increases in integrated EMG activity (iEMG) have been demonstrated with purely eccentric compared with purely concentric training.[41-43] 12 weeks of eccentric strength training of the knee extensors (in men) resulted in a 116% increase in strength with a 188% increase in iEMG compared with a 53% increase in strength and a 28% increase in iEMG with concentric strength training.[42] A subsequent study by Hortobágyi et al.[41] demonstrated similar neural adaptations in women, with only 6 weeks of training. With eccentric training, strength increased by 42% while iEMG increased by 89%. With concentric training, strength increased by 36% and iEMG increased by 39%.

Similarly, Komi and Buskirk[43] found that 7 weeks of eccentric strength training of the elbow flexors in men resulted in a 16% increase in eccentric strength associated with a 22% increase in iEMG, while concentric strength training resulted in a 12% increase in concentric strength associated with a 10% decrease in iEMG. Interestingly, the greatest increases in iEMG with eccentric training occurred at weeks 2 and 3, the point at which the authors noted that the muscle soreness associated with the eccentric training had subsided. It was not clear whether the increase in iEMG was caused by the repeated bouts (6 maximum contractions, 4 days/week) or the initial bouts that resulted in muscle soreness.

Despite strength improvements, force : iEMG ratio was decreased in these studies[41-43] suggesting that eccentric strength training results in a decrease in force per motor unit activation. The fact that Komi and Buskirk[43] noted the largest increase in iEMG at 3 weeks suggests the effect was not due to hypertrophy. This may represent a neural adaptation consistent with the theory of Nosaka and Clarkson[1] whereby the workload for the repeated bouts is distributed over a greater number of active fibres.

Eccentric strength training also resulted in marked cross education to contralateral muscle groups.[44,45] Hortobágyi et al.[44] demonstrated that 12 weeks of unilateral eccentric quadriceps training increased contralateral strength by 77% and iEMG by 54%. Concentric training increased contralateral strength by 30% and iEMG by 28%. Similarly, Weir et al.[45] demonstrated a 16% increase in eccentric strength and a 15% increase in isometric strength in the untrained limb following 8 weeks of unilateral eccentric quadriceps training. These findings[44,45] emphasise the ability of the central nervous system to adapt to eccentric exercise.

2.3 Indirect Evidence for Neural Adaptations

Indirect evidence of a neural adaptation with a repeated bout of eccentric exercise has been demonstrated in several studies.[1,5,7,14] In 2 studies[1,14] a

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repeated bout prior to full recovery did not exacerbate the symptoms, while in other studies[5,7] the initial bout did not have to cause appreciable damage to afford a protective effect. Nosaka and Clarkson[1] had individuals repeat a bout of eccentric exercise after only 3 days when muscle soreness and creatine kinase (CK) levels were significantly elevated. Decreases in soreness and CK on the days following the repeated bout indicated that the protective effect was not dependent on full recovery. Similarly, Mair et al.[14] showed that a repeated bout of eccentric quadriceps exercise after 4 days did not further impair vertical jump or affect CK on the following days. These effects may have been caused by de-recruitment of motor units with injured fibres and increased activity in healthy motor units.

The initial bout of eccentric exercise does not have to cause appreciable damage to provide a protective effect.[5,7] Clarkson and Tremblay[7] had individuals perform 70 maximum eccentric contractions of the elbow flexors with one arm and 24 maximum contractions with the other arm. Two weeks later, the arm that had initially performed 24 contractions now performed 70 contractions. Following the initial bout, changes in strength, pain and muscle soreness were significantly lower in the arm that performed 24 contractions compared with the arm performing 70 contractions. Peak strength loss was 41% in the arm performing 70 contractions compared with 15% in the arm performing 24 contractions. When the arm that had initially performed 24 contractions performed 70 contractions 2 weeks later, strength loss was only 11%. Although the authors suggested that the protective effect may have been a result of increased strength of the cell membrane or surrounding connective tissue, a neural adaptation would also be a plausible explanation.

Brown et al.[5] recently demonstrated results similar to Clarkson and Tremblay.[7] An initial bout of 10, 30 or 50 eccentric contractions of the knee extensors provided equal protection for a bout of 50 contractions 3 weeks later. Marked elevations in CK activity were found on the days following the initial bout of 30 and 50 reps. However, CK activity was not elevated following the initial bout of 10 repetitions. Three weeks later when all individuals performed a bout of 50 repetitions none of the groups demonstrated an increase in CK activity. Similar responses were seen for strength and soreness. While the initial bout of 10 repetitions did not cause appreciable damage, it provided protection from a repeated bout which would have been expected to cause considerable muscle damage. Although not discussed, a neural adaptation to the initial exercise is a plausible explanation since the effects were not dependent on the occurrence of muscle damage. It remains to be determined how many contractions are sufficient to provide a protective effect.

2.4 Evidence Against a Neural Adaptation

The repeated bout effect has been demonstrated with electric stimulation of rat tibialis anterior muscles.[18] In unconditioned muscles, force was 48% of the non-exercised control muscle 3 days after exercise. In eccentrically preconditioned muscles, force was 80% of the control muscles 3 days following repeated bouts (10 or 21 days after the initial bout). The protection afforded to the preconditioned muscles could not be attributed to a neural adaptation since the exercise involved stimulated contractions. While these results prove a peripheral component to the repeated bout effect, a concomitant neural adaptation may occur with voluntary contractions which results in less severe damage. Additionally, the 20% force loss in the preconditioned muscles suggests that the repeated bout still caused significant damage.

3. Connective Tissue Theory

3.1 Mechanical Factors Associated with Muscle Damage

Muscle damage has been referred to as mechanical failure of individual myofibrils consistent with materials fatigue typical of ductile material subjected to cyclic tensile loading.[24,46] Materials fatigue refers to structural failure caused by cumulative tensile

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stress and is distinct from failure caused by the application of a single stress that exceeds the material's ultimate tensile strength. A ductile material under tensile stress experiences plastic deformation prior to failure, in contrast to a brittle material which fails without prior deformation. Skeletal muscle is a ductile material and its behaviour during repeated eccentric contractions is consistent with materials fatigue.[46]

Armstrong et al.[24] have proposed that the passive elements of skeletal muscle experience excessive strain during eccentric contractions at muscle lengths on the 'descending limb' of the length-tension curve. In this situation the ability to produce active tension is decreasing while passive tension is increasing.

Data from isolated whole muscle preparations in animals[47-49] and voluntary contractions in humans[50] have clearly shown that the length of the muscle during eccentric contractions appears to be a critical factor in determining the extent of damage. Lieber and Fridén[49] demonstrated that damage to rabbit tibialis anterior muscles was a function of the length to which the muscle was elongated during stimulation rather than the magnitude of the contractile stimulus. Muscles actively strained 12.5% beyond resting length experienced a 40% decrease in maximum tetanic tension. Muscles strained 25% beyond resting length experienced a 60% decrease in tetanic tension. Newham et al.[50] demonstrated that eccentric contractions of the elbow flexors performed at longer muscle lengths resulted in greater symptoms of muscle damage. On the following day, muscles which exercised from 45° to full elbow extension (long) had 20% strength loss compared with 9% in the muscles exercised from full flexion to 60°. Two days following the initial exercise, muscle tenderness was almost twice as high in the long group. These studies[47-50] support the theory of disruption occurring on the 'descending limb' of the length-tension curve.

3.2 Role of the Intermediate Filaments

The length-tension curve is determined by myofilament overlap which is a function of sarcomere length.[51,52] Sarcomere elongation during eccentric contractions is highly non-uniform with some sarcomeres maintaining length while others are stretched beyond the point of filament overlap.[53-55] This excessive stretch has been referred to as sarcomere 'give'[53] or 'popping'.[55] When a sarcomere is stretched beyond filament overlap ('popped'), a greater dependence is placed on the passive structures to maintain serial tension as the serial sarcomeres shorten.[55] Muscle damage is not a result of the actual 'popping' (which is thought to occur with most eccentric contractions) but is thought to be caused by the cyclic stress placed on the supporting passive structures by continued eccentric contractions following 'popping'.[55] These elements are referred to as intermediate filaments and consist of the proteins desmin, vimentin and synemin.[56,57] The intermediate filaments are responsible for maintaining the structural integrity of serial and parallel sarcomeres.[56-58]

Force transmission within skeletal muscle can be augmented by the intermediate filament system.[58,59] Street[59] demonstrated that the intermediate filament system provides a link to bypass damaged areas and maintain serial force production. While this may be beneficial for maintaining force production during eccentric exercise, the ultimate effect may be to increase subsequent damage. When sarcomeres are stretched beyond myofilament overlap the intermediate filament system must bear the load of subsequent contractions. Repeated loading will result in mechanical failure of the intermediate filament system. Electron microscopic analysis of muscle damage shows significant disruption of the intermediate filaments characterised by Z band streaming and loss of registration of Z bands in parallel myofibrils.[56,57]

The ability of the intermediate filaments to withstand these cyclic stresses may effect the degree of muscle damage resulting from a bout of eccentric exercise. Intermediate filament remodelling may also play a role in the repeated bout effect. In a study of eccentric bicycle ergometry training, Fridén et al.[10] proposed several mechanisms by which the muscle became resistant to damage. It

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was suggested that a structural reorganisation of the intermediate filament system could have prevented further damage. This explanation was offered because intermediate filament repair took 7 to 10 days and this corresponded with the duration of symptoms of muscle damage. Newham et al.[15] demonstrated a repeated bout effect following bouts of maximal eccentric contractions of the elbow flexors separated by 2 weeks. Pain and stiffness following the initial bout was attributed to shortening of the noncontractile connective tissue in parallel with the contractile elements. Adaptation of this connective tissue was proposed as a possible mechanism for the decreased pain and stiffness following repeated bouts. This possibility was restated in subsequent studies[7,8] but no additional supporting evidence was provided.

3.3 Intramuscular Connective Tissue

There is indirect evidence that a connective tissue adaptation can provide protection against muscle damage.[60] Lapier et al.[60] increased the intramuscular connective tissue of rat extensor digitorum longus muscles by immobilising the ankle joint for 3 weeks with the muscle in either a shortened or lengthened position. Muscles immobilised in the lengthened position had 63% more intramuscular connective tissue and 86% lower mass than contralateral control muscles. Muscles immobilised in the shortened position had 47% more intramuscular connective tissue and 21% lower mass than control muscles. Subsequent bouts of stimulated eccentric contractions resulted in 50% force loss in control muscles compared with 40% in muscles immobilised in the shortened position and 8% in muscles immobilised in the lengthened position. The protective effect was attributed to the ability of the increased connective tissue to dissipate myofibrillar stresses. The authors suggested that tissue repair following a damaging bout of eccentric exercise is characterised by a similar increase in intramuscular connective tissue thereby protecting against damage from repeated bouts.

Alternatively, these findings with respect to immobilisation could be interpreted as a cellular adaptation in the muscle tissue. The fact that the effect occurred primarily in the muscles immobilised in the lengthened position suggests that protection may have been a result of the longitudinal addition of sarcomeres (see section 4.3).

An increase in intramuscular connective tissue would be expected to result in increased muscle stiffness.[61] Isometric strength training of the hamstrings has been shown to increase passive muscle stiffness.[62] Klinge et al.[62] demonstrated that a 43% increase in isometric strength was associated with a 25% increase in passive stiffness. It is unlikely that increased tissue cross-sectional area could account for the increased stiffness and the effects were, in part, attributed to connective tissue adaptations. The greater strength improvements and early structural damage with eccentric strength training suggest the possibility of greater connective tissue adaptations than with isometric training.

3.4 Changes in Passive Muscle Stiffness

Passive muscle stiffness has been measured following eccentric exercise.[63-65] Stiffness has been shown to be elevated by as much as 125%[63] and by 138%[64] 2 days following eccentric elbow flexion. Stiffness remained elevated by 61[63] and 42%,[64] respectively, 5 and 10 days after eccentric elbow flexion. Correspondingly, strength remained significantly depressed at these follow-up times. Possible mechanisms for the increase in stiffness include soft tissue oedema, contractile resistance to painful passive extension or injury-induced changes in the mechanical properties of the connective tissues.[63-65] Soft tissue oedema is thought to be important[63] while neuromuscular activity is not thought to play a role.[65] Stiffness changes have not been followed to the point when strength has fully recovered. It is possible that the repair process results in a permanent increase in passive stiffness as a result of remodelling of the connective tissue as suggested by Lapier et al.[60]

In contrast, a recent study examining the effect of fatigue and warm-up prior to a bout of eccentric exercise suggests that decreased muscle stiffness may be protective against muscle damage.[66] In an

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initial experiment, individuals performed 12 maximum eccentric contractions of the elbow flexors with each arm. In one arm the 12 eccentric contractions were preceded by 100 maximum concentric contractions. The concentric exercise resulted in a 20% decrease in isometric strength but did not affect eccentric force production which was similar between arms. In the arm exercising without prior concentric exercise, isometric strength loss was 40% 1 day later and 20% 5 days later. In the arm subjected to prior concentric exercise, isometric strength loss was only 25% 1 day later and had returned to baseline within 5 days. Other indices of muscle damage showed similar differences between arms during the 5 days following the respective exercise bouts. Paradoxically, these results suggested that whole muscle fatigue (induced concentrically) protected the muscle from damage. The authors performed an additional experiment to help explain these effects.

In the second part of the study the eccentric exercise was preceded by 100 concentric elbow flexions without resistance to simulate warm-up exercise. The eccentric exercise preceded by warm-up resulted in significantly less strength loss and minimal changes in CK activity compared with the eccentric exercise without prior warm-up. These protective effects of prior concentric exercise (fatiguing and nonfatiguing) were attributed to decreased passive muscle stiffness. This is supported by data from Magnusson et al.[67] who demonstrated a 20% reduction in passive hamstring stiffness immediately following 40 maximum concentric contractions. Alternatively, a change in motor unit recruitment following warm-up and fatigue could explain the results of Nosaka and Clarkson.[66] While these data demonstrate a protective effect, they do not provide an insight into a mechanism for the repeated bout effect.

4. Cellular Theory

4.1 Sarcomere Disruption

Sarcomere disruption is characterised by Z band streaming with associated A band disruption.[56] In addition, there is a loss of lateral registration of parallel myofibrils.[56] 20% of fibres were disrupted 3 days following an initial 30-minute bout of eccentric cycling with only 4% of fibres disrupted 4 weeks later, following several repeated bouts.[10]

At the cellular level muscle contraction occurs by the sliding filament action caused by the cyclic formation of actin-myosin crossbridges.[52] During isometric and concentric contractions, adenosine triphosphate (ATP) is required to detach crossbridges. However, during eccentric contractions, crossbridges are forcibly detached without splitting ATP.[52] The term ‘popping’ has been used to describe what happens when a sarcomere is strained sufficiently that all crossbridges are forcibly detached and there is no longer any myofilament overlap.[55] As previously stated (section 3.1), sarcomere length changes are thought to be highly non-uniform during eccentric contractions.[53-55] Morgan’s theory[55] predicts that some sarcomeres are ‘popped’ while others maintain length or actually shorten. Upon relaxation most sarcomeres recover interdigitation but some of them remain overextended. With repeated eccentric contractions more sarcomeres are ‘popped’. These ‘popped’ sarcomeres are repeatedly strained and the cell membrane is ultimately disrupted.

Evidence in support of this theory was provided by Wood et al.[68] who demonstrated that strength loss in the frog sartorius muscle immediately following a series of eccentric contractions was associated with a shift to the right in the length-tension relationship. These findings are consistent with the intact sarcomeres adopting a shorter length subsequent to strain of disrupted sarcomeres. Electron micrographs of damaged sarcomeres provided additional support. More recently, Saxton and Donnelly[69] demonstrated greater strength loss at short muscle lengths in human elbow flexors following a bout of eccentric exercise. The disproportionate strength loss at short muscle lengths was also attributed to intact sarcomeres adopting a shorter length subsequent to strain of disrupted sarcomeres.

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4.2 Potential Cellular Adaptations

Cellular adaptations explaining the repeated bout effect may occur at the level of the muscle fibre, the myofibril or the sarcomere itself. Proposed theories include strengthening of the cell membrane,[7] removal of a pool of weak fibres or sarcomeres following the initial damage[6,14,70] and longitudinal addition of sarcomeres.[10,13]

Clarkson and Tremblay[7] suggested that strengthening of the cell membrane could be an alternative explanation to a connective tissue adaptation. Sarcolemmal disruption results in the loss of calcium homeostasis which initiates the cellular necrosis evident on electron micrographs.[24] Strengthening of the sarcolemma or the sarcoplasmic reticulum could prevent disruption during eccentric contractions thereby preventing the calcium influx and avoiding the subsequent cellular necrosis.

Injury following downhill running in rats was explained by Armstrong et al.[70] as disruption of a pool of stress 'susceptible' fibres. Accordingly, reduced injury following repeated bouts of downhill running[6] and eccentric quadriceps exercise[14] has been explained by the removal of the 'susceptible' fibres following the initial injury. Removal of a pool of stress 'susceptible' myofibres or sarcomeres, as opposed to whole fibres, would be more consistent with the electron micrographic evidence of damage. The initial bout may serve to identify and remove a select population of weak sarcomeres. The lack of further damage when the repeated bout occurs before full recovery supports such a theory.[1,14] However, a limitation to this theory is the fact that the initial bout does not have to cause appreciable damage in order to provide a protective effect.[3,5,7] If the weak sarcomeres are still intact and functional then they should be disrupted by the repeated bout and damage would be evident. This was clearly not the case in the studies by Schwane and Armstrong,[3] Brown et al.[5] and Clarkson and Tremblay.[7]

4.3 Direct Evidence for Cellular Adaptation

Since muscle damage can be explained in terms of sarcomere mechanics it is plausible that the repeated bout effect could be explained by an adaptation in sarcomere mechanics. Such a theory was proposed by Morgan[55] whereby longitudinal addition of sarcomeres following an initial bout of eccentric exercise would reduce sarcomere strain for a given muscle excursion during a repeated bout. Reduced sarcomere strain would allow the myofilaments to maintain overlap, limit sarcomere 'popping' and avoid the ensuing cellular disruption.

The possibility that repair of muscle damage occurs by serial addition of sarcomeres within a myofibril was previously discussed by Fridén et al.[10] Electron microscopic observations of biopsies from vastus lateralis muscles of women following 8 weeks of eccentric bicycle ergometry indicated lengthening of the myofibrils by addition of new sarcomeres.[10] However, the authors failed to elaborate on their observations and did not provide any specific evidence of such an adaptation.

More recently Lynn and Morgan[13] tested Morgan's theory of longitudinal addition of sarcomeres by comparing the number of serial sarcomeres in rat vastus intermedius muscles following either uphill or downhill running. One week of training with downhill running resulted in an 8% increase in serial sarcomeres compared with a sedentary control group. Similar uphill training resulted in a 4% decrease in serial sarcomeres relative to control rats. These results directly support Morgan's original theory[55] and provide a specific cellular mechanism for the repeated bout effect.

The plausibility of this theory depends on the time course for the cellular adaptation and the stimulus required to initiate the adaptation. As previously mentioned, human studies have demonstrated a repeated bout effect prior to full recovery from the initial bout.[1,14] All criterion measures indicated significant muscle damage 3 days following an initial bout of eccentric exercise yet a repeated bout at that time did not exacerbate the damage.[1] In fact, indices of muscle damage were reduced following

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the repeated bout. Morgan's theory would not be plausible in this instance since the sarcomeres were given inadequate time to regenerate. Additionally, Morgan's theory predicts that the initial myofibrillar disruption is the stimulus for the addition of sarcomeres. However, as stated before (section 2.3), the initial bout does not have to cause appreciable damage in order to provide a protective effect.[3,5,7]

The concept of sarcomere strain as the initial step in the initiation of muscle damage is supported by a shift in the length-tension curve to the right immediately following a series of eccentric contractions.[68] If longitudinal addition of sarcomeres occurs, one would expect the length-tension curve to be shifted to the right following repair. With more sarcomeres in series a greater muscle length would be required to reach optimal sarcomere length. However, the length-tension curve has been shown to return to normal within 5 hours in toad sartorius muscles[68] and within 2 days in human triceps surae muscles.[71]

5. Other Mechanisms

Force loss following eccentric contractions may not be entirely caused by mechanical disruption. Impairment of calcium-mediated E-C coupling has been shown to contribute to force loss following active stretches of isolated whole muscle[22] and single fibre preparations[21] from mice. These results[21,22] suggest impaired calcium release or sensitivity following myofibrillar disruption. An adaptation in E-C coupling may explain the reduced strength loss following a repeated bout. Strengthening of the sarcoplasmic reticulum, as suggested by Clarkson and Tremblay,[7] may prevent impairment of E-C coupling with a repeated bout.

Reduced muscle damage following a repeated bout has been attributed to a blunted inflammatory response.[16] Decreased neutrophil and monocyte activation were seen on the days subsequent to the repeated bout. It was not clear whether these effects reflected a blunted immune response to tissue damage, or the lack of tissue damage following the repeated bout. An adaptation in the inflammatory response may explain the lack of further damage when the repeated bout is performed prior to recovery from the initial bout.[1,14]

6. Future Directions

Although a plethora of data exist on the neural basis of muscle fatigue (for a review see Enoka and Stuart[72]), very little data are available on the neural basis of muscle damage. Low motor unit activation during eccentric contractions has been implicated in the occurrence of muscle damage[27] but has not been specifically studied. Additionally, recruitment patterns during eccentric contractions have not been examined with respect to the subsequent damage. The possibility of selective recruitment of fast twitch fibres for eccentric exercise remains controversial but may in part explain preferential damage to those fibres. Despite several studies suggesting a neural adaptation to explain the repeated bout effect,[1,12,14,16] no studies have tested such an hypothesis.

Muscle damage has been described as mechanical failure of individual myofibrils subjected to cyclic tensile loading.[24,46] Surprisingly, the mechanical properties of muscle have not been examined in relation to muscle damage. Data from Lapier et al.[60] suggest that increased passive stiffness may be protective against muscle damage and may explain the repeated bout effect. In contrast, recent indirect evidence from Nosaka and Clarkson[66] suggest that decreased passive stiffness may be protective. However, the specific effects of passive muscle stiffness on the initiation of muscle damage and the repeated bout effect have not been examined.

Studies examining the role of muscle length[47-50] and longitudinal addition of sarcomeres[13] suggest that the ability to maintain myofilament overlap during eccentric contractions is critical to limiting damage. The possibility that an increase in crossbridge binding strength could prevent sarcomere 'popping' and maintain myofilament overlap during eccentric contractions has not been examined. Quick release techniques in stimulated isolated muscle fibres have been used to measure the elastic elements (stiffness/compliance) within the

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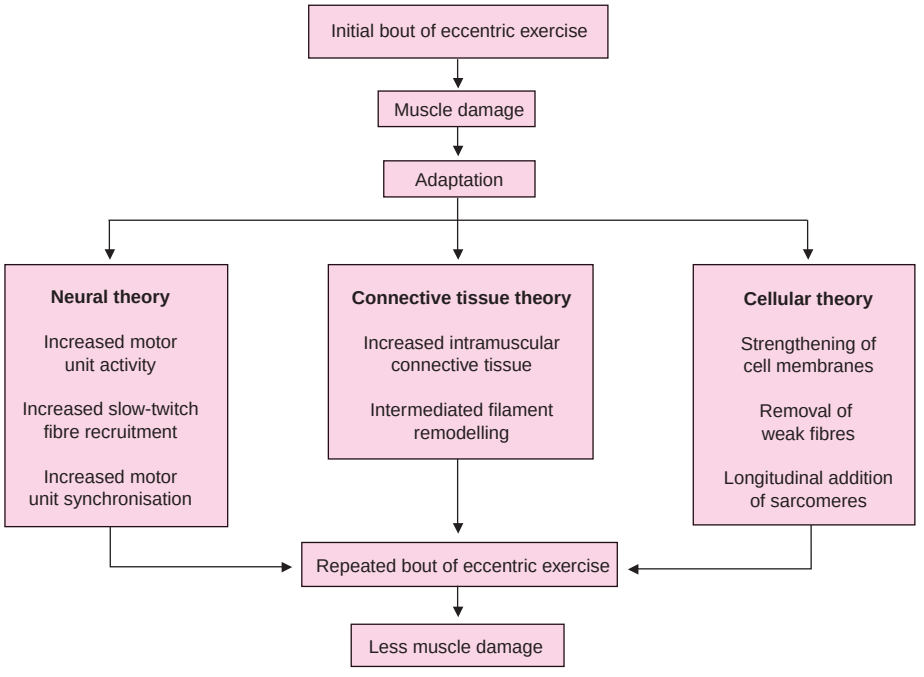

Fig. 1. Potential mechanisms which may explain the repeated bout effect.

crossbridges.[52,73] However, in whole muscle, contributions from the tendon cannot be ruled out.[74,75] Using the quick release technique, Pousson et al.[76] demonstrated a 10 to 20% reduction in compliance of the elbow flexors, at fixed submaximal loads, following 6 weeks of eccentric training. It was not possible to distinguish between an adaptation in the tendon or an adaptation in the contractile material. Although the authors favoured the latter explanation, an increase in crossbridge binding strength could have accounted for the observed effects. Similar effects have not been studied with respect to the repeated bout effect.

7. Conclusions

Despite the numerous studies that have clearly demonstrated the repeated bout effect there is little consensus in the literature as to the actual mechanism. Various neural, connective tissue and cellular theories have been discussed (fig. 1). It is clear that one theory cannot explain all of the various demonstrations of the repeated bout effect found in the literature. The fact that the effect was demonstrated with electrically stimulated contractions in an animal model precludes an exclusive neural adaptation. However, connective tissue and cellular adaptations seem unlikely in studies that demonstrated a repeated bout effect prior to full recovery. Additionally, the fact that the initial bout does not have to cause appreciable damage in order to provide a protective effect does not support connective tissue or cellular adaptations. It is possible that the repeated bout effect occurs through the interaction of various neural, connective tissue and cellular factors that are dependent on the particulars of the eccentric exercise bout and the specific muscle groups involved.

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