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INVITED REVIEW

The 'muscular wisdom' fatigue hypothesis: historical perspectives and contemporary challenges

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Abstract
Identifying mechanisms of force loss (i.e., muscle fatigue) has been of long-standing interest. The muscular wisdom hypothesis (promulgated circa 1970) states the declining motor unit firing rates during a sustained maximal voluntary contraction do not contribute to force loss, but rather, i) lower rates provide appropriate excitation as contractile speed slows with fatigue, and ii) provides protection against peripheral conduction failure. This theory was predominant until further scrutiny and experimental evidence in the ensuing decades made it less clear whether the hypothesis was justified properly. Therefore, a central tenet in our understanding is whether the declining firing rates observed during maximal contractions are causative or preventative of force loss. Here we provide a historical perspective of the studies antecedent to the original hypothesis and an up-to-date comprehensive review of the factors involved. Overall, we summarize and evaluate the evidence as to whether force loss during maximal contractions is due to inadequate neural input or impairments in peripheral contractility. Alterations in motor unit function, (as 'the final common pathway') are the focus to explore these concepts from an integrated approach. Although some aspects may have been originally overstated, due mostly to a lack of a fuller understanding of various factors at the time, we conclude the decline in motor unit firing rates are preventive and not causative of force loss during sustained maximal contractions. Overall, the muscle wisdom hypothesis is a classic example of the capable adjustments in response to stress by mitigating impairments at one site through adaptations at another.

Keywords Muscle fatigue · Motor unit firing rate · High-frequency fatigue · Electromyography · Electrical stimulation · M-wave

Abbreviations

EMG	Electromyography
FDI	First dorsal interosseous
HFF	High-frequency fatigue
MU	Motor unit
MVC	Maximal voluntary contraction
HFF	High-frequency fatigue

Communicated by Michalis G Nikolaidis.

Dedicated to the memory and works of Brenda R. (Bigland) Ritchie (1927–2019).

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Introduction

Prolonged muscle activation leads to an objective reduction of the contractile response (e.g., force) that is reversible with rest and historically termed muscle fatigue. Depending on the task, the diminishing contractile response is met with many adaptations from the nervous system (Gandevia 2001; Taylor et al. 2016; Amann et al. 2022). Indeed, some of these adaptations may counteract or mitigate the reductions in contractile output (Bigland-Ritchie et al. 1983a; Marsden et al. 1983; Bigland-Ritchie and Woods 1984; Bigland-Ritchie 1993).

In addition to the loss of force during a sustained isometric maximal voluntary contraction (MVC) there is a concurrent reduction in motor unit (MU) firing rates. Indeed, the loss of force and decline in firing rates are well paralleled, and both may reduce by ~ 50% during a sustained 1-min MVC (Bigland-Ritchie et al. 1983a, b; Grimby et al. 1981a, b; Grimby and Hannerz 1977; Marsden et al. 1983 cf. Macefield et al. 2000). Originally it was hypothesized that the

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reduction in firing rate *preserves* rather than *contributes* to force loss (Jones et al. 1979; Bigland-Ritchie 1981, 1993; Marsden et al. 1983; Bigland-Ritchie and Woods 1984). This led to the concept of muscular wisdom; a term that was promoted by Marsden et al. 1983 (although an abstract was presented under the title 'muscular wisdom' by the same authors at the 1968 Physiological Society meeting, see Marsden et al. 1969). The primary evidence to support these claims originated from several experiments conducted by the separate groups of B. Bigland-Ritchie, D.A Jones, and colleagues as well as C.D Marsden, J.C Meadows, and P.A Merton.

The primary proposal by which the reduction in firing rates serves to minimize force loss was founded on two principles: i) protection against peripheral conduction failure (i.e., 'high-frequency fatigue') and ii) optimization of force output in response to slowing contractile speed. It was stated "the first factor puts a premium on slowing and the second factor allows it to happen without penalty" and thus the "frequency of motor discharge has to fall in order to get the best out of the muscle" (Marsden et al. 1983). As highlighted by others, "it is clearly beneficial if the CNS can keep excitation rates as low as possible, without compromising force" (Bigland-Ritchie et al. 1995). Although sensible upon conception (e.g., discussions within *Human muscle fatigue: physiological mechanisms*, 1981) and an "intrinsically appealing" (Gandevia 1993) hypothesis, subsequent evidence did not support this view (Fuglevand and Keen 2003), and the rationale has been scrutinized (Enoka and Stuart 1992; Stuart and Callister 1993; Fuglevand and Keen 2003) resulting in statements that the hypothesis "does not hold" (Taylor and Gandevia 2008) and requires "systematic investigation" (Stuart and Callister 1993).

This narrative review will: i) introduce central and peripheral aspects of force loss; ii) provide an in-depth summary of the experiments that led to the muscle wisdom hypothesis; iii) summarize data that do not support the hypothesis; iv) outline limitations of experimental evidence for and against the hypothesis; v) conclude the current state of the hypothesis, and provide future directions.

Definitions

This review summarizes and provides a historical perspective of muscle fatigue (i.e., loss of contractile capacity due to sustained activation) from the last ~ 100 years. Over this time terminology has evolved with more recent taxonomies proposed.

However, to maintain consistency with the original prominent works summarized, here, we define muscle fatigue as a reduction in contractile output (e.g., force or power) in response to muscle activation, regardless of whether the task can be sustained (Bigland-Ritchie et al. 1995), but is reversible with rest (Allen et al. 2008). Indeed, at this time this simple and pointed definition prompted the comment "the insistence that fatigue is defined for operational purposes in terms of force has clearly been valuable for the progress of neurophysiology" (E.J.M Campbell, post-presentation discussion p.g. 171 in Human Muscle Fatigue: Physiological Mechanisms, 1981). Within the past ~ 10 years the term muscle fatigue has been challenged as not appropriate or misleading with more nuanced distinctions and definitions having been proposed (Kluger et al. 2013; Enoka and Duchateau 2016; Behrens et al. 2023). Despite these corrections and to limit the blurring of terminology between reduced preparations and human tasks, we will use the term muscle fatigue, but being mindful of updated classifications. Furthermore, with a focus on the history of the muscle wisdom hypothesis, it would be disingenuous to the many studies cited to alter their original terminology in relation specifically to the current theme of muscular wisdom.

Force loss due to contractile activity can be categorized as being mediated by 'central' or 'peripheral' factors (Gandevia 2001) which well represent the language in the original articles highlighted herein. Central fatigue is defined as a progressive reduction in voluntary activation of a muscle during exercise; whereas peripheral fatigue is produced by changes at or distal to the neuromuscular junction (Gandevia 2001). This distinction allows for site separation with the use of peripheral nerve stimulation. Indeed, much of the work to quantify 'central fatigue' relied on force comparisons between voluntary and maximally stimulated tetanic contractions (R.H.T Edwards, post-presentation discussion p.g. 156 in Human Muscle Fatigue: Physiological Mechanisms, 1981).

Historical perspective on central and peripheral factors of muscle fatigue

It has been of great interest and debate as to whether force loss originates from central factors (e.g., supraspinal), peripheral factors (i.e., at or distal to the neuromuscular junction), or both. Here we provide a non-exhaustive summary of experiments antecedent to the development of the muscle wisdom hypothesis to introduce factors involved in force loss and where controversies exist.

When a single electrical shock of a peripheral nerve is superimposed on voluntary efforts the force amplitude elicited is inversely related to the initial voluntary force. As voluntary force approaches a maximum no force increase is observed in response to the stimulation. This finding was described by Merton in 1954 and has since been replicated (e.g., Belanger and McComas 1981); and suggests that the central nervous system is capable of maximal muscle fibre activation during voluntary efforts (cf. Kavanagh et al. 2019; Amann et al. 2022). Furthermore, this maximum could be interpreted with linear extrapolation from submaximal efforts (Merton 1954; Belanger and McComas 1981; Rice et al. 1992).

When Merton employed this interpolated twitch technique during a *sustained* (> 30 s) isometric MVC there was no instance during which a superimposed single pulse increased force output, despite the declining voluntary force. Furthermore, when a single electrical pulse is applied to a peripheral nerve a synchronized electrical potential is produced and can be recorded with electromyography (EMG). This response (i.e., M-wave) represents the summated electrical activity of all MUs within the recording area of the electrode. Because there was no reduction in M-wave response it was interpreted that there was no limitation of conduction or neuromuscular failure despite substantial loss of force.

Indeed, maximal voluntary and electrically stimulated forces similarly declined with sustained activation (Merton and Pampiglione 1950). These experiments prompted the statements, "when strength fails electrical stimulation of the motor nerve cannot restore it" (Merton 1954), and later "anyone who possesses a sphygmomanometer and an open mind can readily convince himself that the site of this fatigue is in the muscles themselves" (Merton 1956). Merton suggested force loss was a peripheral phenomenon within muscle fibres and defective alterations in the biochemistry of the contractile process were the likely cause (Merton 1954). However, this was not unanimously shared as others argued that "overriding importance has been attached by Merton to failure of the contractile mechanism in fatigue" (Krnjević and Miledi 1958).

Despite the experimental evidence, many results published did not support the findings of Merton. During sustained tetanic nerve stimulation of cat muscle, force loss was closely paralleled to the decline in the 'action current' size recorded over the surface of the muscle (Davis and Davis 1932). This was also observed with sustained tetanic stimulation in human and rabbit muscle, in which the loss of force was always reported with a decrease of intramuscular action potentials (i.e., M-waves) (Naess and Storm-Mathisen 1955). Both groups speculated some form of neuromuscular junction fatigue had occurred (Davis and Davis 1932; Naess and Storm-Mathisen 1955). At the time, evidence for a causative relation between action potential size and force loss came from frog cardiac muscle in which "there is no evidence that the height of the electrical response can be reduced without affecting that of the mechanical response" (Yule Bogue and Mendez 1930, cf.Sandow 1952; Steiman 1943).

In a set of experiments by Brown and Burns (1949) muscles of the cat were maximally stimulated up to 250 pulses/s, and as force declined neuromuscular block was assessed by alternating between nerve (i.e., requiring neuromuscular junction transmission) and direct muscle excitation (i.e., no neuromuscular junction transmission) or vice versa. During sustained tetanic nerve stimulation in which force was declining, switching to direct muscle stimulation (maintaining the same stimulation frequency) increased force at regular intervals over a 20 s contraction. Furthermore, force declined when direct muscle stimulation was switched to nerve stimulation during identical experiments. Indeed, the force increase by switching from nerve to direct muscle stimulation had a linear relationship with stimulation frequency. Thus, the largest improvements in force were observed at higher stimulation rates indicating that neuromuscular block was frequency dependent. It was speculated there were more muscle fibres left idle by insufficient transmission at the highest frequencies of stimulation. When nerve stimulation was switched to direct muscle stimulation, the activation of these idle fibres could almost completely compensate for the loss in force (Brown and Burns 1949). Indeed, it was proposed that impairments in neuromuscular transmission may serve as protection for the contractile elements (Naess and Storm-Mathisen 1955; Krnjević and Miledi 1958). This is in contrast with the conclusions by Merton, who suggested skeletal muscle does not have a "functional reserve" because significant force loss can be observed despite, with what was interpreted as, maximal muscle fibre activation (Merton 1954).

To test whether changes in neuromuscular transmission contributed to force loss Merton compared twitch responses through peripheral nerve stimulation and with that of 'direct' muscle stimulation in a human which was accomplished using an exorbitant voltage of 2400 V. After a 4 min MVC, twitch responses were similarly reduced whether twitches were evoked with peripheral nerve stimulation or direct muscle stimulation. Furthermore, the M-wave response was unaltered and therefore electrical transmission was maintained. Therefore, Merton concluded that action potential propagation was not greatly affected by sustained contractions, but rather acted on a weakened peripheral contractile system (Merton et al. 1981).

In sum, Merton stated the literature was "bedevilled" with accounts that support force loss is not due to impairments in the peripheral contractile elements (Merton 1956). Indeed, many experiments which supported impaired neuromuscular transmission as a cause of force loss were performed with unphysiological tetanic stimulation. Earlier observations by Reid concluded that force loss induced by *voluntary* contractions was "primarily central" (Reid 1927, 1928). Furthermore, in those experiments it was acknowledged that central and peripheral factors can overlap and the relative contribution to force loss is dependent on the task. A concept that has been well-appreciated for more than the last 30 years (e.g., Amann et al. 2022; Bigland-Ritchie et al. 1995; Enoka and Stuart 1992; Gandevia 2001).

Reid demonstrated that during repetitive isometric MVCs of middle finger flexion central and peripheral contributions to force loss were dependent on the contraction frequency. At 100 contractions a minute, both voluntary and electrically stimulated force (stimulation rate not specified but initial force was close to voluntary) declined. Conversely, at 30 contractions a minute voluntary force declined, however, electrically stimulated force was maintained. Therefore, the slower series of contractions had a primarily central aspect (i.e., inability to voluntarily activate muscle fibres) of force loss, whereas force loss during the rapid series of contractions displayed central and peripheral impairments. Thus, the origin of force loss is dependent on the fatiguing task.

In a separate set of experiments, force loss was assessed during maximal isotonic contractions (3 kg with a contraction rate of 24/min) until the weight could hardly be moved. Although voluntary force could not move the load, median nerve stimulation (stimulation rate not specified) restored force to ~ 50% of initial and moved the load sufficiently. These data indicated some form of central fatigue contributed to force loss during the isotonic task. The experiments by Reid clearly support a central component of force loss, and the relative contributions depends on the fatiguing task.

In Merton's experiments, a single electrical shock produced a similar M-wave as the baseline and no improvement in force during a sustained, force-declining MVC. Furthermore, during recovery twitch force was impaired despite maintenance of the M-wave. Therefore, the contractile output was less responsive to motor impulses despite preserved neuromuscular transmission, suggesting force loss was a peripheral phenomenon within the muscle fibres. During an identical sustained MVC, but with blood flow occluded, there was also no improvement in force during single shock stimulation despite maintenance of the M-wave. However, during a period of rest, twitch force only recovered once blood flow was restored, despite the maintenance of M-wave amplitude. This further supported fatigue being within the muscle fibres and thus did not involve central aspects or impaired neuromuscular transmission.

With blood flow also occluded Reid (Reid 1927, 1928) demonstrated that following repetitive maximal isotonic contractions (2 kg at 30 contractions a minute) until the load could barely move, electrical stimulation moved the load and restored force to ~ 40% of the initial. Therefore, force loss during this task clearly included a central component and those earlier results did not align with the findings of Merton despite both experiments using blood flow occlusion. Merton suggested his experiments with blood flow occlusion "abolished" the concept of central fatigue or neuromuscular block contributing to force loss (Merton 1954). However, as described, Reid's experiments which did include blood flow occlusion supported an aspect of central fatigue.

To explain these differences, Merton suggested small movements (such as middle finger flexion employed by Reid) is a skillful task and thus may induce some central fatiguing aspect, unlike the short-term strength dependence (i.e., sustained MVCs) of his experiments. This remark seems not completely justified as one might suggest a similar skill requirement for thumb adduction which was used for Merton's experiments. Including the muscle group tested, key differences between the experiments were intermittent compared to sustained contractions and the use of single shocks or tetanic rates of stimulation. Nevertheless, it seems likely both central and peripheral factors can contribute to force loss and the relative contribution is dependent on the task. In the experiments of Reid, EMG was not monitored and thus action potential transmission could not be assessed (Reid 1927, 1928). It is also important to discuss experimental difficulties in which Merton later described himself as "callow" and that results were a "happy cancellation of errors" (Marsden et al. 1983). Furthermore, in the original force device used by Merton force increments of ~ 5% were difficult to detect, compared to modern systems which are 1%, or less (Gandevia et al. 1995; Gandevia 2001 for a detailed review).

Twenty years after Merton's publications it was reported by Stephens and Taylor (1972) that during a sustained 60 s MVC there was a ~ 50% decline in force with a concurrent reduction of the smooth rectified surface EMG signal and a reduction to 65% of baseline for the M-wave area. These data were interpreted as evidence for action potential transmission failure during voluntarily induced fatigue, which was contrary to Merton, but comparable with earlier reports of electrically stimulated tetanic contractions (Davis and Davis 1932; Brown and Burns 1949; Naess and Storm-Mathisen 1955). However, the difference between Stephens and Taylor and Merton may be due to differences in the muscle groups tested (e.g., Clamann and Broecker 1979; Zijdewind and Kernell 1994). This concept and other potential explanations of discrepancies are expanded below ('Electrical propagation of muscle during sustained maximal voluntary contractions').

The reduction of the smooth rectified surface EMG signal during sustained MVCs (e.g., Stephens and Taylor 1972) does not unanimously occur across participants and may be muscle dependent (Bigland-Ritchie et al. 1978; R.H.T Edwards, post-presentation discussion p.g. 155 Human Muscle Fatigue: Physiological Mechanisms, 1981). In one study, three of nine participants showed a more rapid reduction of voluntary knee extension force compared to stimulated (50 Hz) and thus central fatigue was evident (Bigland-Ritchie 1981). Additionally, surface rectified EMG declined in this group of participants, but this reduction was not apparent for the participants that did not show differential force loss between voluntary and stimulated force (i.e., no central fatigue). However, in the group in which central fatigue was evident, brief voluntary 'extra efforts' could restore force and increase smooth rectified EMG (Bigland-Ritchie et al. 1978; Bigland-Ritchie 1981). It is important to note most studies on humans herein are conducted in what is described as "well-motivated subjects" (R.H.T Edwards, post-presentation discussion p.g. 155 in Human Muscle Fatigue: Physiological Mechanisms, 1981). The findings with brief 'extra efforts' emphasize the challenge of motivation with voluntary contractions. Indeed, to mitigate this aspect it was suggested central fatigue should be defined as "something that could *never* be overcome voluntarily, even briefly" (B. Bigland-Ritchie, post-presentation discussion p.g. 155 in Human Muscle Fatigue: Physiological Mechanisms, 1981).

Based on discrepancies among studies it was clear that "there is little agreement as to the underlying mechanisms involved or at which sites failure may occur" (Jones et al. 1979). These opposing findings formed the basic premise for the experiments which prompted the muscle wisdom hypothesis.

Mechanisms for force loss during sustained maximal activation

Here we provide a brief synopsis of contemporary factors proposed to impair force generation during sustained high-intensity activation.

During MVCs muscle circulation is greatly impaired and therefore, as a high-intensity contraction is sustained the active muscle is non-perfused and can become ischemic (Barcroft and Millen 1939; Vøllstad et al. 1988). This hypoxic environment due to local circulatory arrest hinders the removal of metabolic byproducts, which are greatly implicated in muscle fatigue. Data from permeabilized ('skinned') muscle fibres have indicated elevations of both inorganic phosphate and H^+, which occurs *in* vivo (Cady et al. 1989), synergically impair peak force (Cooke 2007; Nelson et al. 2014; Sundberg et al. 2018) likely through eliminating high-force cross-bridge interactions (Woodward and Debold 2018). In contrast to permeabilized single fibres, intact fibres can be stimulated to induce force loss and simultaneous measurements of force and cytosolic free Ca^{2+} can be made (Cheng and Westerblad 2017). During repetitive intermittent activation of fast-twitch muscle at high frequencies, impaired myofibrillar function has been shown to be the primary mechanism for early force loss but decreased sarcoplasmic reticulum Ca^{2+} release becomes more significant as activation is sustained (for review see Allen et al. 2008; Cheng et al. 2018). Therefore, at the single muscle fibre level impaired cross-bridge and Ca^{2+} kinetics are prominent causes for force loss.

Both Na^+ and K^+ play an important role in membrane excitation and thus are essential for muscle contraction (for review McKenna et al. 2024). With each muscle action potential, there is an influx of Na^+ and a net efflux of K^+ ions across the cell membrane. If sufficient time between potentials is provided normal extracellular cation concentrations are re-established, however, quick repetitive excitation will substantially alter ionic content which may contribute to force loss (Cairns et al. 2022). With repetitive activation impaired action potential propagation can occur due to Na^+ depletion (Bezanilla et al. 1972; Cairns and Dulhunty 1995) and extracellular K^+ accumulation (Juel 1986; Medboø and Sejersted 1990; Cairns et al. 1995). These changes in action potential propagation may impair excitation–contraction coupling at various sites such as the sarcolemma voltage-sensors or t-tubules which will not completely engage impairing Ca^{2+} release and subsequent acto-myosin interactions (Fuglevand 1995). However, several mechanisms (see section '*Additional mechanisms for counteracting electrical propagation impairment*') in addition to the reduction of MU firing rates help maintain normal electrical propagation and thus this potential impairment during voluntary contractions is likely not large (see section '*Electrical propagation of muscle during sustained maximal voluntary contractions*').

During sustained MVC there are reports of MU firing rate cessation or decruitment of MUs (Grimby et al. 1981a; Marsden et al. 1983; Peters and Fuglevand 1999) and thus muscle fibres could be left inactive and therefore would not contribute to whole muscle force. This is supported (Gandevia et al. 1996; cf. Bigland-Ritchie et al. 1982) with reports of diminished muscle activation assessed with the interpolated twitch technique (for review see Gandevia 2001). This potential inability to maintain recruitment of MUs can be due to various factors including suboptimal activation of descending inputs (Gandevia et al. 1996) as well as a decrease in excitatory (faciliatory) feedback with a concurrent increase in inhibitory feedback (Bigland-Ritchie et al. 1986; Bongiovanni and Hagbarth 1990; Macefield et al. 1991); which ultimately reduces motoneuron excitability (Butler et al. 2003; McNeil et al. 2009). Collectively these factors may impair MU recruitment and thus the amount of activated muscle fibres contributing to whole muscle force.

As detailed above (see 'Introduction') MU firing rates decline during sustained high-intensity activation and the mechanisms involved are likely similar to those proposed to impair MU recruitment (i.e., decruitment, noted above). However, unlike whether MUs (or muscle fibres) are activated, which have a direct effect on force generation; the way in which these fibres are activated (i.e., firing rate) and the respective implications for force generation are more complex, and several factors must be considered. Therefore, a central question underlying this review is whether declining MU firing rates observed during maximal contractions are causative or preventative of force loss.

Development of the muscle wisdom hypothesis

D.A Jones, B. Bigland-Ritchie, and colleagues

In companion papers, Jones, Bigland-Ritchie and colleagues (Bigland-Ritchie et al. 1979; Jones et al. 1979) provided evidence supporting the muscle wisdom hypothesis. The primary intention was to separate potential sites contributing to force loss during sustained muscle activation. To accomplish this, sustained voluntary and electrically stimulated contractions at various frequencies were employed in humans in addition to stimulation of isolated mouse muscle. In some muscles from humans, MVC force can be equaled by artificial electrical stimulation at high rates (e.g., 80 Hz). Partly for this reason ulnar stimulation of the adductor pollicis was performed in their original studies in addition to being the only muscle employed in adduction of the thumb.

Maximal ulnar nerve stimulation at 80 Hz was required to match MVC force output, but, 20 Hz stimulation produced ~ 70% of MVC force. Sustained stimulation at 80 Hz for 60 s decreased force output to ~ 20% of baseline values. Conversely, 20 Hz stimulation elicited minimal force impairment after 60s. Despite the lower force production with the 20 Hz stimulation, for contractions > 35 s the area under the force–time curve was greater for 20 Hz compared to 80 Hz stimulation. Therefore, more time under tension occurred with sustained low-frequency stimulation compared to high-frequency stimulation when matched for contraction duration. Thus, sustained stimulation at the lower frequency was more fatigue-resistant than the higher frequency (Fig. 1A).

In subsequent experiments, the sustained 80 Hz stimulation was interrupted with brief trains at 20 Hz. After 12 s of 80 Hz stimulation, force declined ~ 25%, however, at this time 20 Hz stimulation showed no decline in force compared to baseline values. After this, stimulation at 20 Hz produced *greater* force than 80 Hz when interrupted throughout the 60 s contraction (Fig. 1B). Therefore, opposite to the baseline state of the muscle, the lower frequency stimulation (20 Hz) produced greater force than the high-frequency (80 Hz). This provided evidence that during sustained muscle activation lower stimulation rates were beneficial for maintenance of force, while high rates were detrimental.

Separately, sustained 60 s MVCs were briefly interrupted by 3 s stimulation at either 80 or 20 Hz. After 12 s the 80 Hz stimulation was matched to the declining MVC force. However, the force in response to 80 Hz was ~ 50% of MVC force by 28 s and this relationship was maintained at 42 and 55 s. Therefore, there was no instance when the 80 Hz stimulation increased force output, and after the initial 12 s in all cases the high-frequency stimulation decreased force output. Therefore, it was interpreted that the muscle was always fully active during the sustained MVC, despite declining force. Before the sustained MVC 20 Hz stimulation was ~ 65% of MVC force. At 12 and 28 s, force at 20 Hz modestly increased relative to baseline values while MVC force declined. At 42 s the force in response to 20 Hz was impaired relative to its' baseline, however, 20 Hz force was now matched to MVC force, and this continued throughout the final 18 s. These data indicated that during acute force loss lower frequencies of activation are required to match MVC force. Conversely, high frequencies produce less force than both low frequencies of stimulation and MVC; and thus, high stimulation rates are detrimental for force production during sustained activation.

At the time of these experiments, very little was known about maximal MU firing rates, especially during sustained fatiguing contractions. Indeed, the most relevant data were from 'aberrant' MUs recorded in adductor pollicis which showed a progressive slowing with sustained activity (Marsden et al. 1971). Therefore, to the test hypothesis that sustained high-frequency stimulation was detrimental to force output, a condition with a declining stimulation rate (to match voluntary MU firing rate reports e.g., Marsden et al. 1971) was employed.

This consisted of separate trials of a 60 s sustained MVC and an electrically stimulated contraction. For the stimulated contraction the frequency was initially at 60 Hz, but progressively declined to 20 Hz by 30 s and after which 20 Hz was maintained for the final 30 s. Force loss during the two trials was identical. Furthermore, the force loss during both trials was much less than sustained stimulation at 80 Hz. Therefore, stimulation rate reduction was beneficial throughout a sustained tetanic contraction as force loss was minimized compared to constant high-frequency simulation. Furthermore, to match the force loss of an MVC with a tetanic contraction the initially high stimulation rate must be reduced throughout the contraction time course. Therefore, reducing stimulation rate (or firing rate) was deemed important in mitigating force loss.

From the experiments in humans in the first study (Jones et al. 1979) it was concluded that: i) high-frequency stimulation is required to match baseline MVC force, however, stimulation at this rate leads to greater force loss than low-frequency stimulation in which force is well maintained; ii) brief interruption of high-frequency stimulation during sustained MVCs causes impaired force generation, but stimulation at a lower frequency maintains force generation; iii) force loss during a sustained MVC is less than sustained high-frequency stimulation and MVC force loss can only be matched when an initially high stimulation rate declines with

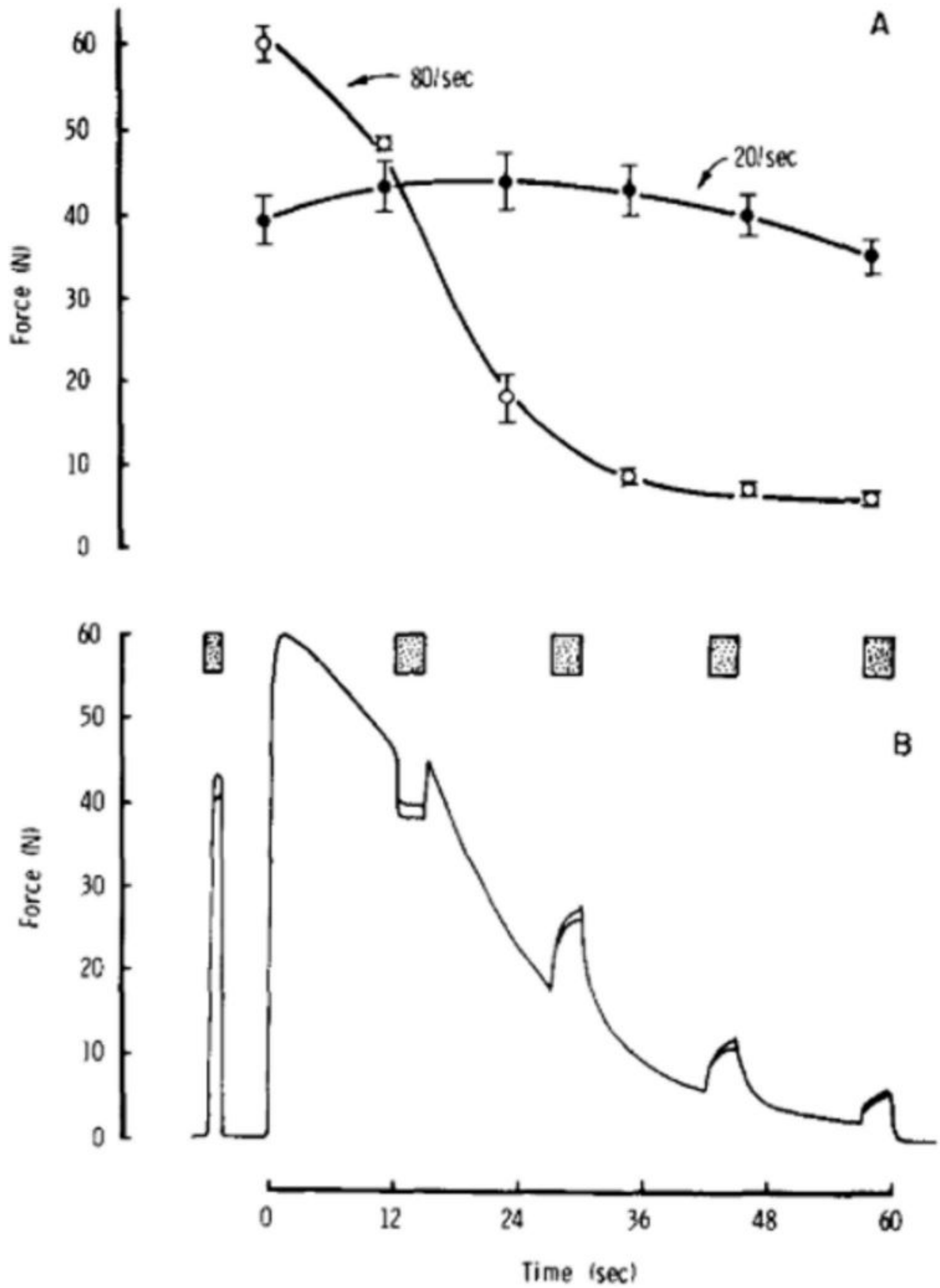

Fig. 1 Human thumb adductor force (N) in response to prolonged stimulation (60s) at 80 and 20 Hz. Panel A: data are mean ± standard deviation. Open and closed circles represent stimulation at 80 and 20 Hz, respectively. Panel B: Force tracing of prolonged 80 Hz stimulation interrupted by 20 Hz (shaded bars). Figure adapted from (Jones et al. 1979) (reprinted with permission)

contraction time; iv) in no instance did stimulation increase force during a sustained MVC and thus force loss cannot be attributed to reduced neural input.

As outlined above, there were reports of neuromuscular junction failure to some degree during sustained tetanic stimulation (e.g., Naess and Storm-Mathisen 1955; Krnjević and Miledi 1958). Therefore, to eliminate this as a potential site of force loss, Jones & colleagues conducted additional experiments in isolated curarized mouse muscle (Jones et al. 1979). This preparation was used for direct muscle stimulation, compared to peripheral nerve stimulation which does not exclude the neuromuscular junction. The mouse soleus muscle was used as its fibre type distribution is more similar to human muscles than other muscle groups (e.g., Augusto et al. 2004). Comparable experimental protocols were undertaken following the design of the experiments in humans noted above.

In isolated mouse muscle, with continuous stimulation at 100 Hz (high-frequency) for 50 s force declined to 10% of baseline values. At 50 s when the frequency was lowered to 20 Hz force rapidly increased to 50% of 100 Hz baseline force values and this was maintained for the final

30 s. Conversely, after 50 s of continuous 50 Hz (moderate frequency) stimulation force declined to 50% of baseline values. When the stimulation frequency was lowered to 20 Hz the force did not increase, however, the force loss was halted, and this was maintained for the final 30 s. Therefore, reducing stimulation frequency during direct muscle stimulation of mouse muscle clearly enhanced force generation during sustained muscle activation, similar to their prior findings in humans.

The authors speculated changes in extracellular ion concentrations may contribute to the varying levels of force loss across different frequencies of stimulation. To assess the effect of extracellular [Na^+] reduction on force during sustained tetanic contractions the mouse muscle medium was replaced with equimolar choline$^+$. This experimental model was adapted so that extracellular [Na^+] could be directly modified and controlled, which is unavailable in a in vivo human model of the previous experiments. Experiments in the mouse model consisted of 50 Hz stimulation for 50 s, immediately followed by 20 Hz for 30 s (Fig. 2). A reduction from the normal condition of 161mM extracellular [Na^+] to 92 and 45 mM resulted in a minimal change in force loss during the initial 20 s. Thereafter, force loss was rapid, and the rate of decline was roughly proportional to the reduction in [Na^+]. The greatest reduction in [Na^+], 24 mM, displayed a rapid decline in force to about 10% over the initial 20 s of simulation. When the stimulation frequency was lowered to 20 Hz for the final 30 s, force loss was halted for both the 161 and 92 mM conditions. For the 45 and 24 mM conditions,

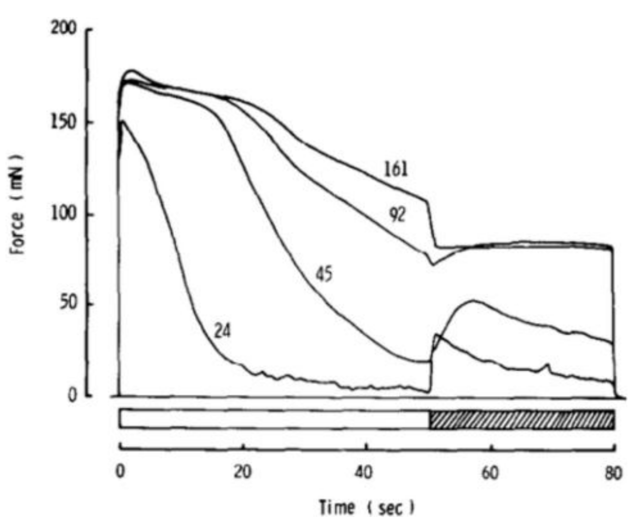

Fig. 2 Force (mN) tracings of isolated curarized mouse soleus muscle stimulated at 50 Hz for 50s. At 50 s stimulation frequency was reduced to 20 Hz for 30 s (shaded bar on the x axis). The [Na^+] of the tissue medium was replaced with equimolar choline$^+$ to assess the effect of extracellular [Na^+] reduction on force. The millimolar Na^+ concentrations are within the figure for each force tracing. Figure adapted from Jones et al. 1979 (reprinted with permission)

the 20 Hz stimulation increased force production and force loss was not halted but minimized. These results mimicked the results in integrated human muscles and clearly showed a benefit in force production when the stimulation rate was reduced during prolonged muscle activation (Fig. 2).

Furthermore, the data from isolated curarized mouse muscle provides some mechanistic insight and suggests that reduced extracellular [Na^+] impairs or reduces the probability of action potential propagation across the sarcolemma and or t-tubular system. As direct muscle stimulation was used the curarized mouse muscle force loss was independent of the neuromuscular junction, and thus this site was likely not the cause of fatigue. This is also supported by single isolated frog fibres in which extracellular [Na^+] depletion in the bathing medium decreased tension through activation failure of primarily central myofibrils. The activation failure and drop in tension were proportional to the [Na^+] depletion and the frequency of stimulation (Bezanilla et al. 1972). Furthermore, force loss during tetanic stimulation was reduced when extracellular [Na^+] was *increased* in rat soleus bundles (Cairns and Dulhunty 1995). The combination of these results clearly indicated an impairment in muscle activation and thus force generation due to electrical propagation impairment at the muscle in response to lowering extracellular [Na^+].

A primary conclusion of the first paper (Jones et al. 1979) is that force loss is minimized with a decreasing stimulation rate, compared to continuous stimulation at a high rate. Based on experiments in isolated curarized mouse muscle it was proposed frequency reduction minimized force loss by minimizing peripheral conduction failure. This is likely due to differences in intra- and extracellular ion concentrations during sustained high compared to low stimulation frequencies (e.g., Cairns and Dulhunty 1995). However, the first study of the companion papers (Jones et al. 1979) did not record electrical activity, and these conclusions were based on mechanical force responses. To address this concern, similar experiments were conducted (study 2) with recordings of surface EMG during prolonged voluntary and electrically stimulated muscle activation (Bigland-Ritchie et al. 1979).

Thus, in the subsequent study, continuous ulnar nerve stimulation was done for 60 s at constant frequencies of 20, 50 and 80 Hz. During the 20 Hz stimulation, there was no decrease in force and a minimal reduction in the M-wave amplitude. Both smooth rectified surface EMG and M-wave area increased throughout the 60 s which was due to prolongation of the individual action potentials, likely from slowing of muscle conduction velocity. Slowed muscle conduction velocity has been consistently reported during voluntary and electrically stimulated contractions (e.g., Juel 1988).

Force was reduced to ~ 30% of baseline in the 50 and 80 Hz conditions at the end of the 60 s. During the first 20 s smooth rectified surface EMG increased before rapidly decreasing in the 50 Hz trial. In the 80 Hz trial smooth rectified surface EMG increased in the initial 5 s before a rapid decline. In both instances, the increase in smooth rectified surface EMG was due to increased M-wave area which was likely from the concurrent slowing of conduction velocity. After the initial potentiation effect (e.g., Hicks and McComas 1989; McComas et al. 1993), M-wave amplitude rapidly declined and eventually could not be distinguished in either trial. Therefore, action potential propagation failure was observed in response to sustained high-frequency activation (i.e., 50 and 80 Hz) but not low-frequency (i.e., 20 Hz). This electrical transmission failure was the likely causative of force loss during the high-frequency trials, but not the low-frequency trial as there was no decline in force and a minimal reduction in the M-wave (Fig. 3B).

This concept was further supported by subsequent experiments. After 45 s of continuous 80 Hz stimulation force and M-wave area declined to ~ 30% of baseline values. When 20 Hz stimulation was applied at this time force increased to ~60% of baseline 80 Hz force, like the initial study (Jones et al. 1979). However, in addition to the recovery of force, M-wave area increased and recovered to almost the baseline value (Fig. 3A). Therefore, the recovery of force occurred in conjunction with electrical transmission recovery.

During a 60 s MVC, a single maximal shock was performed every 10 s to assess the M-wave response. Despite force loss the amplitude of the M-wave was minimally affected. As shown previously, when an initially high stimulation rate is decreased throughout contraction time, force loss matches a sustained MVC (Jones et al. 1979). During this intervention (declining stimulation rate from 60–20 Hz) the evoked M-wave amplitude was not reduced, similar to the MVC condition, however, this is the opposite of the sustained high-frequency stimulation trial (Fig. 3B). Thus, reducing the stimulation rate during a tetanic contraction matched both the force decay and M-wave (i.e., electrical activity) of a sustained MVC (Fig. 4). These data indicated the reduction in activation rate during a sustained MVC was beneficial for force preservation by limiting peripheral transmission failure. Additionally, force loss during MVC is not related to impaired electrical transmission of the periphery.

C.D Marsden, J.C Meadows, and P.A Merton

Some works regarding the muscle wisdom hypotheses by Marsden and colleagues were published before the studies of Jones, Bigland-Ritchie, and colleagues (Bigland-Ritchie et al. 1979; Jones et al. 1979). However, these were published as brief conference abstracts at the Physiological Society meeting (Marsden et al. 1969, 1971, 1976) but were considered "widely read" (Nordstrom et al. 2007). It was not until 1983 that these works were described in detail in a textbook chapter (Marsden et al. 1983), with the authors stating the experiments were mainly conducted in the early 1970s.

Similar to Bigland-Ritchie et al. (1979) and Jones et al. (1979) electrical stimulation of the ulnar nerve was used to contract the thumb adductor, and several key observations were comparable across the groups of authors.

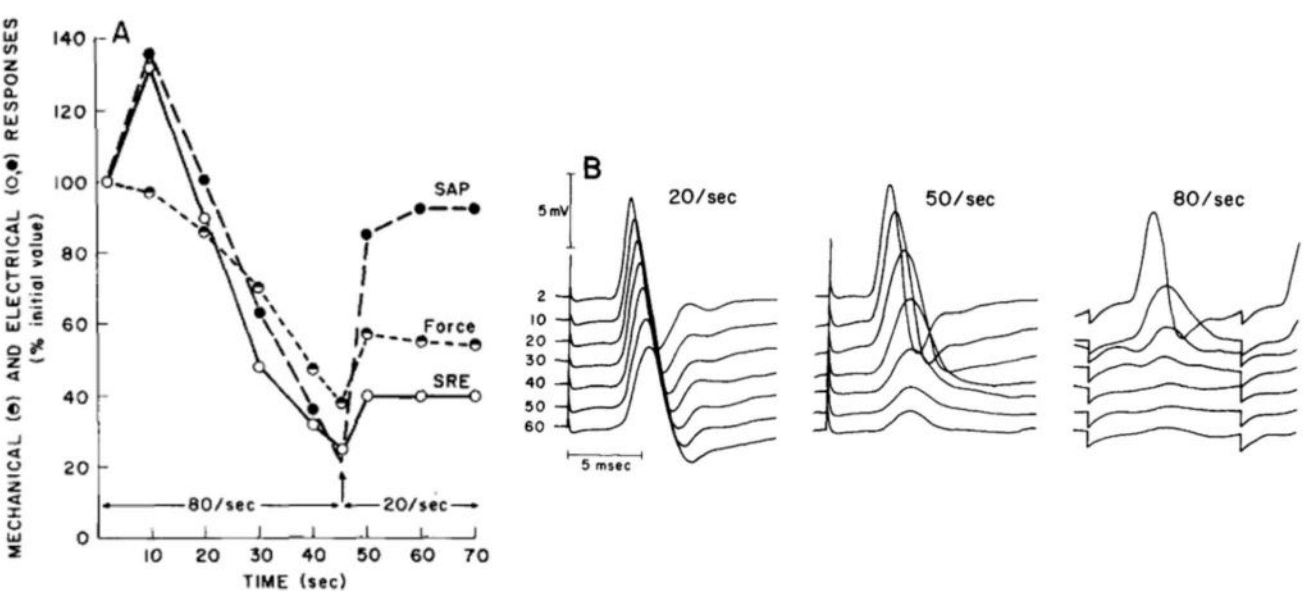

Fig. 3 **A** Changes in force (% initial value, half-filled circles) and surface electromyography during electrical stimulation (% initial value). Thumb adduction stimulated at 80 Hz for 45 s then switched to 20 Hz (upwards arrow denoted on x axis). SAP: surface action potential area (filled circles); SRE: Smooth rectified electromyography (open circles). **B** Exemplar M-wave responses (mV) recorded over the adductor pollicis at 2 s and then at 10 s intervals during electrical stimulation at 20, 50 and 80 Hz. Figure adapted from (Bigland-Ritchie et al. 1979) (reprinted with permission)

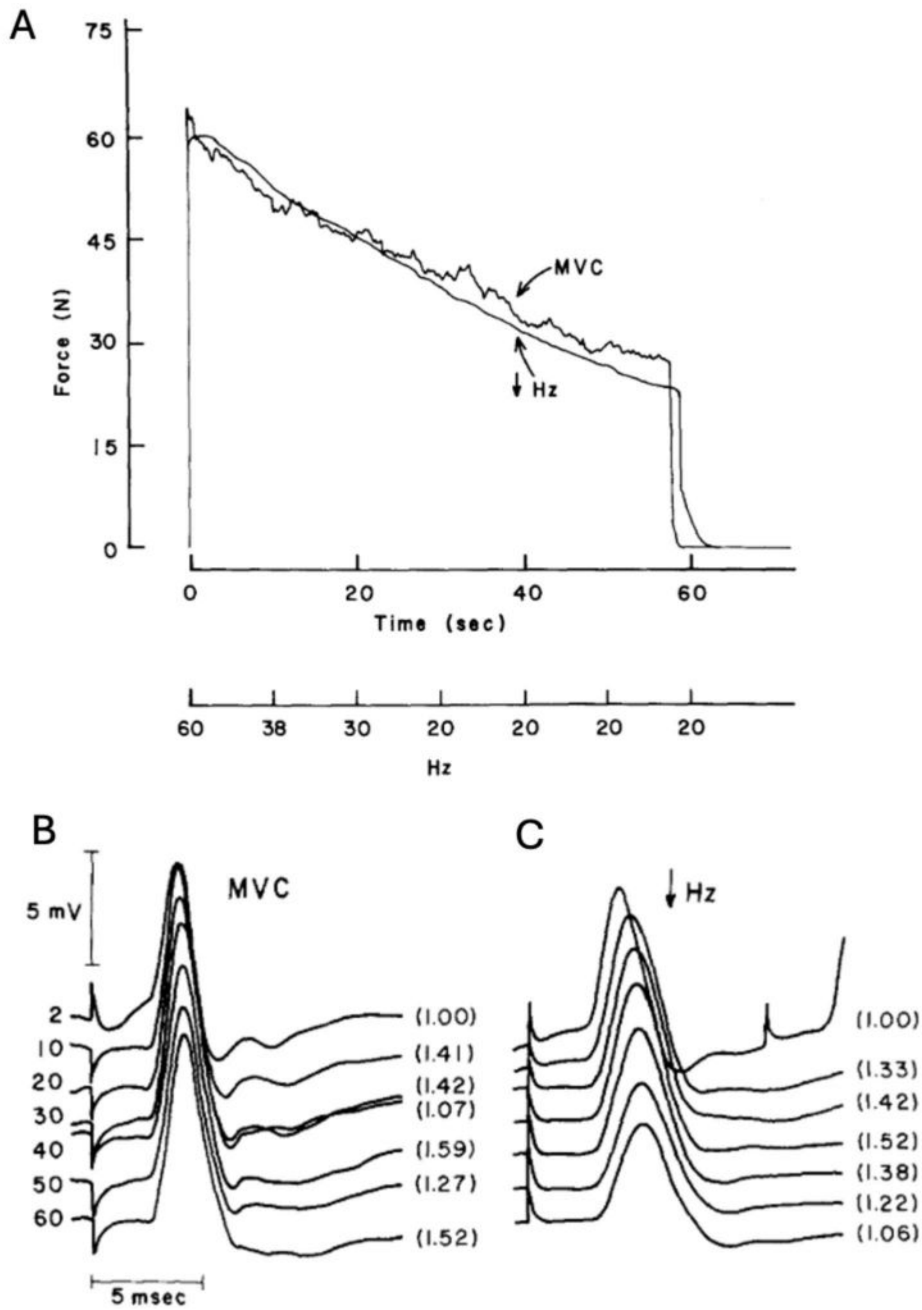

Fig. 4 **A** Comparison of force (N) during a sustained thumb adduction maximal voluntary contraction (MVC) and during electrical stimulation with progressively declining rates noted in the figure on the x-axis. **B** M-wave responses (mV) recorded over the adductor pollicis at 2 s and then at 10 s intervals during MVC or **C** electrical stimulation with progressively declining rates (denoted in the x-axis of panel **A**). Figure adapted from Bigland-Ritchie et al. 1979; Jones et al. 1979 (reprinted with permission)

Sustained stimulation at 100 Hz for 95 s caused a greater and more rapid reduction in force compared to a sustained MVC. Furthermore, when the stimulation rate was initially 60 Hz but declined to 20 Hz throughout the contraction time course (60 Hz for 8 s, 45 Hz for 17 s, 30 Hz for 15 s, 20 Hz for 55 s) force loss matched a sustained MVC condition. This protocol was termed 'artificial wisdom'. Thus, like Jones and Bigland-Ritchie, sustained high-frequency stimulation caused a greater force loss than a sustained MVC. Furthermore, for a sustained tetanic contraction to match the force loss of an MVC the initially high stimulation rate must be reduced throughout the contraction time course. Indeed, Marsden and colleagues agreed with Jones and Bigland-Ritchie and provided similar interpretations that the activation rate of the muscle must decline during sustained contraction to avoid or delay peripheral conduction failure (referenced by these authors as 'activation failure').

As an alternative approach, force was plotted against the number of stimulated impulses delivered rather than contraction time (Fig. 5). This prompted the statement from Merton that "electricity has everything to do with isometric fatigue and chemistry has nothing to do with it" (P.A Merton, post-presentation discussion p.g. 152 in Human Muscle Fatigue: Physiological Mechanisms, 1981). For this comparison, the

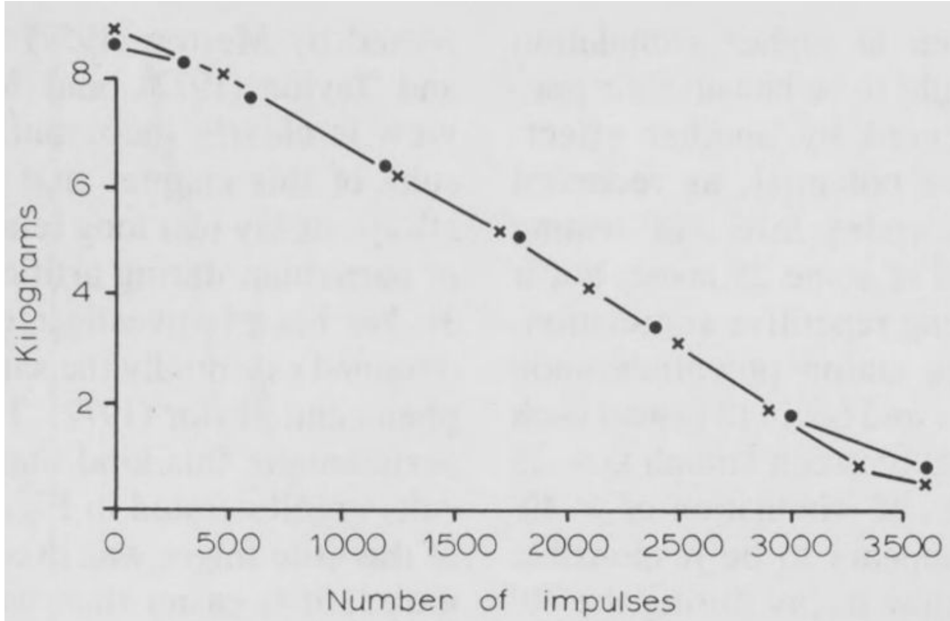

Fig. 5 Comparison of force (kilograms) during sustained 60 s electrical stimulated contraction at 60 Hz and 'artificial wisdom' where rates started at 60 Hz eventually declining to 20 Hz. Despite the difference in rates both conditions were matched for a total number of impulses (3600). The artificial wisdom stimulation was 60 Hz for 8 s, 45 Hz for 17 s, 30 Hz for 15 s and 20 Hz for 95 s, totaling 2 min and 15 s. The sustained 60 Hz stimulation lasted 1 min. Circles and x symbols indicate the sustained 60 Hz and 'artificial wisdom' condition, respectively. Figure from Marsden et al. 1983 (reprinted with permission)

number of impulses (3600) were matched rather than the contraction duration. The high-frequency condition consisted of sustained 60 Hz stimulation, lasting 1 min. The artificial wisdom condition started at 60 Hz declining at various time points eventually to 20 Hz, it took 2 min 15 s to reach 3600 impulses.

With absolute force on the y-axis and number of impulses on the x-axis the two conditions produced an identical relationship (Fig. 5). This demonstrated force output was solely dependent on the impulses delivered, not the activation rate. If the impulses are spread out to optimize muscle activation, fatigue resistance is improved, in this case the force–time area under the curve increased ~ 2 times. These data indicated the total number of impulses the muscle receives are the primary determinant of force loss, rather than contraction duration, and that "force depends solely on the number of shocks delivered" (P.A Merton, post-presentation discussion p.g. 153 in Human Muscle Fatigue: Physiological Mechanisms, 1981). In discussions of these data at the Ciba Foundation symposium on human muscle fatigue (1981), it was also noted maintenance of force using the minimum number of muscle reactivation would be energetically advantageous (C.M. Wiles, post-presentation discussion p.g. 153 in Human Muscle Fatigue: Physiological Mechanisms, 1981). Therefore, a reduction in MU firing rates would clearly be advantageous in mitigating force loss during a sustained MVC.

A similar approach matching total impulses (3600) was conducted but with a range of sustained frequencies from 5–200 Hz with simultaneous recordings of force and surface EMG (Fig. 6). As expected at contraction onset the initial force was dependent on the frequency of activation. However, after ~ 1500 impulses force loss was entirely a function of the number of impulses delivered and not the frequency of stimulation as the force was similar across all frequencies at 20 Hz and above (Fig. 6). Thus, independent of the wide ranges of excitation frequency and contraction duration the total number of impulses determined force loss.

At ~ 1000 impulses M-wave responses always declined during sustained stimulation from 5–40 Hz, and the final decline was similar across these frequencies. Furthermore, after ~ 1500 impulses the rate of force decline began to accelerate. Thus, these findings demonstrated activation failure occurred at lower frequencies of activation but developed much more slowly than at high rates of activation (Fig. 6). These data suggested the slowing of MU firing rates during a sustained MVC, or the 'artificial wisdom' stimulation, would delay activation failure but could not avoid it entirely. The results are interesting but have been described as "puzzling" and "require confirmation and extension" (Stuart and Callister 1993). This confirmation has not yet been established.

At stimulation rates of 80 and 200 Hz the M-wave response declined rapidly at contraction onset. In a rested human muscle, the M-wave is ~ 25 ms (Marsden et al. 1983) in duration and is also known to increase during fatigue (e.g., Bigland-Ritchie et al. 1979; Juel 1988). Therefore, at high stimulation rates, the M-wave begins to collide and cancels out. This phenomenon likely explains why the M-wave response dramatically declined without major losses of force (Fig. 6). This concept is expanded in greater detail below ('Is the muscle wisdom hypothesis still justified?').

Collectively these data (Fig. 5, 6) clearly indicate the rate of activation, rather than contraction duration, was the primary determinant of force loss. Therefore, minimizing the

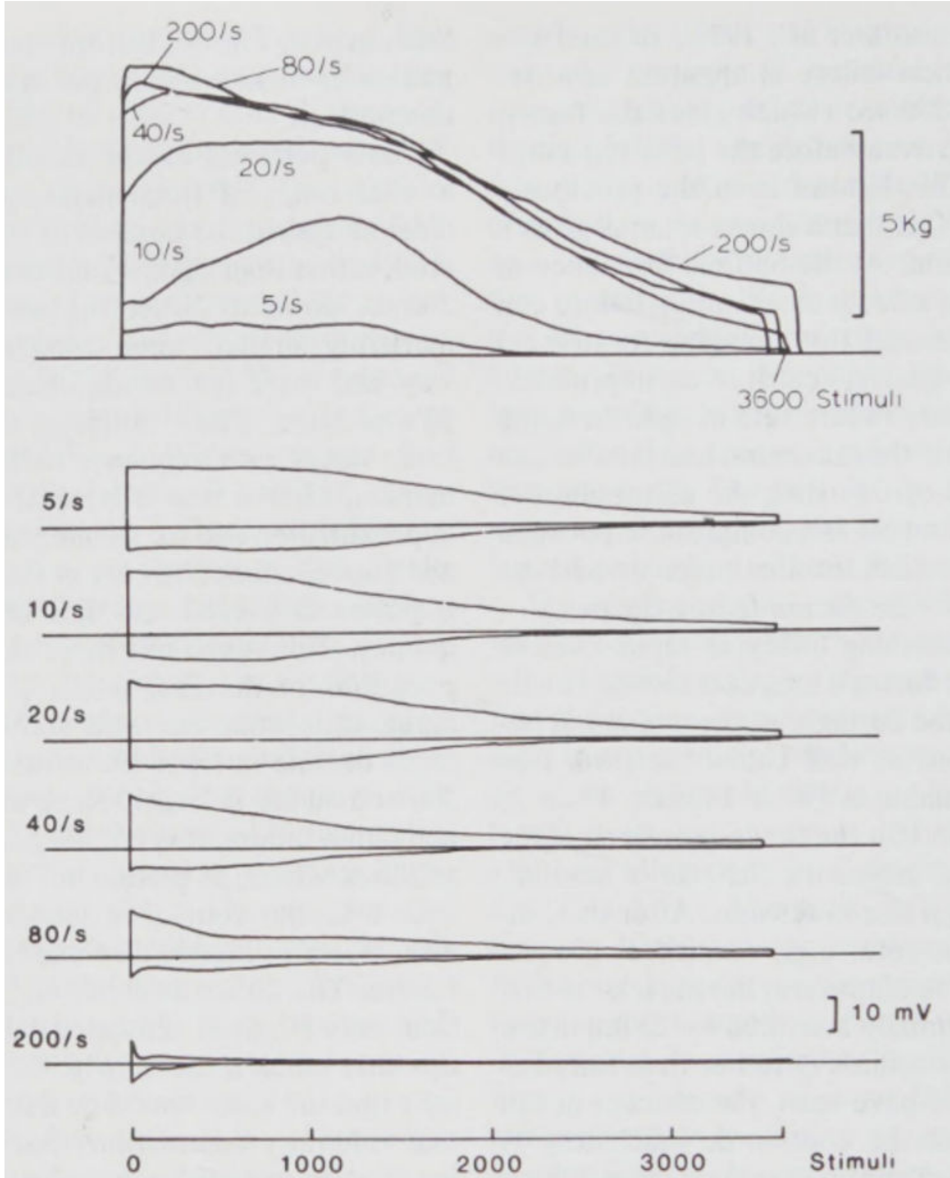

Fig. 6 Force (kg) and M-wave responses evoked at a range of constant frequencies from 5 to 200 Hz (denoted on y-axis). Force is plotted against the number of stimulation pulses which was matched at 3600 irrespective of the stimulation frequency (total contraction time ranging from 18 s to 12 min). Force (kg) tracings for each stimulation rate are plotted in the top panel. The bottom panel represents envelopes of the M-wave responses of the adductor pollicis evoked during stimulation at each respective rate. Figure from Marsden et al. 1983 (reprinted with permission)

rate of activation is an important strategy to prolong muscle activation and minimize force loss.

Contractile speed and force summation

The relationship between intrinsic contractile speed, activation rate, and force summation has been a long-appreciated feature of skeletal muscle. In skate and rabbit muscle, Raniver initially demonstrated that in response to a single electrical shock red colored muscles contracted slower than pale muscles (reviewed by Kronecker and Stirling 1878). In response to repetitive stimulation, the pale muscle demonstrated poor summation of force compared to the red muscle because of the differences in contractile speed.

In reduced preparations with intracellular recordings and injected current there is a correlation between the frequency of motoneuron firing and the twitch speed of the innervated muscle fibres (Kernell 1979). Therefore, higher motoneuron firing rates were observed when the muscle fibres twitch properties were faster and vice versa (Kernell 1979, 1995). Comparable results were reported in human MUs during voluntary contractions as the MU afterhyperpolarization phase was positively correlated with electrically evoked twitch contraction duration (Gossen et al. 2003). Furthermore, stimulation of single human MUs has shown that the frequency required to evoke 50% of the maximal tetanic response was related to twitch contraction time (Thomas et al. 1991b; Macefield et al. 1996). That is, higher rates of activation were required for MUs with faster twitch contraction times. This 'speed-match' (Gardiner and Kernell 1990) is also apparent across muscles which demonstrate significant differences in contractile speed. For example, in humans, soleus twitch responses (tibial nerve stimulation with the knee flexed) are ~ 50% slower than the biceps brachii and adductor pollics. During brief non-fatiguing maximal contractions, MU firing rates match the differences in contractile speed as soleus rates were ~ 11 Hz compared to ~ 30 Hz in the biceps brachii and adductor pollics (Bellemare et al. 1983). Indeed, this matching also exists within single MUs of a muscle displaying a range of contractile speeds such that "each motor unit fires at its fusion frequency in voluntary contraction" (Grimby et al. 1979).

For optimal force generation, the motoneuron firing rate should be well-matched to the contractile speed of the innervated muscle fibres (Burke 1981). As suggested by many, any frequency above this optimal relationship would be "uneconomical" (Bigland-Ritchie 1981) and provide " no effective return in a higher contraction tension" (Eccles et al. 1958). Indeed, as highlighted above, the evidence across various preparations supports the concept of 'speed matching' (Gardiner and Kernell 1990; Kernell 1995).

During a sustained MVC the loss of force and reduction in MU firing rates are well paralleled and thus it is tempting to suggest the firing rate reduction is causative of force loss (Bigland-Ritchie 1981). However, in addition to force loss contractile slowing may also occur during sustained muscle activation at higher intensities (e.g., Davis and Davis 1932). Indeed, both the loss of force and slowed relaxation occur simultaneously during a sustained MVC (Bigland-Ritchie et al. 1983a; Bigland-Ritchie and Woods 1984).

As contractile speed slows during a sustained MVC force summation and tetanic fusion occur at lower rates of activation (Fig. 7; Davis and Davis 1932; Bigland-Ritchie et al. 1983a; Bigland-Ritchie and Woods 1984) and therefore declining firing rates would maintain a fully fused tetanus (Marsden et al. 1971). In 1932 with electrical stimulation of cat muscle, Davis and Davis concluded, "fusion of twitches into a smooth tetanus usually occurs at a lower frequency in the fatigued than in the fresh muscle" (Davis and Davis 1932). Indeed, sustained rates above those necessary for a fully fused tetanus would not enhance force and could *contribute* to force loss due to peripheral excitation failure (Bigland-Ritchie 1981) as suggested by the experiments summarized earlier (Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983). Additionally, maintenance of high rates would be metabolically uneconomical (C.M. Wiles, post-presentation discussion p.g. 153 in Human Muscle Fatigue: Physiological Mechanisms, 1981). Therefore, the slowing contractile speed suggests that firing rates must decline to maintain optimal maximal muscle activation (Marsden et al. 1971, 1983; Bigland-Ritchie et al. 1983a; Bigland-Ritchie and Woods 1984).

Immediately following a 60 s MVC, electrically evoked twitch relaxation rate is 50% slower compared to before the MVC (Fig. 7, Bigland-Ritchie et al. 1983a, b; Bigland-Ritchie and Woods 1984). Indeed, due to contractile slowing there is greater force summation during sub-tetanic rates of stimulation (e.g., 7 Hz) and consequently the sub-tetanic force is a greater proportion of maximal tetanic force (Fig. 7, Bigland-Ritchie et al. 1983a, b; Bigland-Ritchie and Woods 1984). Furthermore, the slowing of contractile speed and decline in population-derived MU firing rates during a sustained MVC are roughly parallel (Bigland-Ritchie et al. 1983a; Bigland-Ritchie and Woods 1984), indicating that fusion would not be compromised.

To better understand the relationship between contractile slowing and the reduction in activation rate during sustained

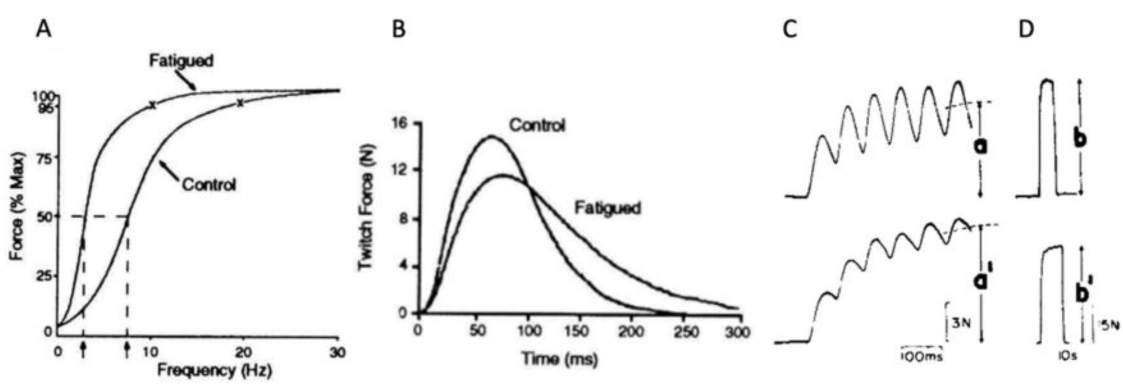

Fig. 7 **A** Electrically evoked force-frequency relationship before (control) and after a fatiguing task. Upward arrows on x-axis indicate the stimulated frequency required to evoke 50% maximal force. X symbols indicate the frequency required to evoke 95% of maximal force. **B** Electrically evoked muscle twitch response before (control) and after a fatiguing task. **C** and **D** Unfused tetani (7 Hz, **C**), and tetanic (50 Hz, **D**) responses from the adductor pollicis before (top panel) and after (bottom panel) a fatiguing task. After fatigue the twitch relaxation slows (**B**) and the force in response to 7 Hz stimulation (a/a) increased ~ 15%. The fraction of maximum force (a/b) increased ~ 17 to ~ 24%. Figures adapted (Bigland-Ritchie and Woods 1984; Bigland-Ritchie 1993) (reprinted with permission)

contractions, Marsden and colleagues cooled the adductor pollicis from ~ 36 to 24 °C (Marsden et al. 1983), causing slowed contractions and thus greater force summation was observed at lower frequencies of excitation. Consequently, a leftward shift in the stimulated force-frequency relationship was observed.

Three fatigue tasks were performed with the muscle at room temperature and cooled. All tasks were 100 s and consisted of a sustained MVC, artificial wisdom (i.e., 60–20 Hz stimulation), and slowed artificial wisdom. The slowed artificial wisdom condition had the same time intervals between frequency decline as the standard artificial wisdom trial except the absolute frequencies were lowered starting at 40 Hz and declining to 10 Hz.

At room temperature, the artificial wisdom stimulation and the sustained MVC were well matched for force loss, as expected (Bigland-Ritchie et al. 1979; Jones et al. 1979). Throughout most of the contraction time course, the slowed artificial wisdom task had a lower force output, however, force at 100 s was similar across all three tasks. Like at room temperature the artificial wisdom stimulation and the sustained MVC were well matched with the muscle cooled. During the slowed artificial wisdom condition force loss was similar to the MVC and artificial wisdom condition during the first 10 s. However, after this the slowed artificial wisdom condition had greater force and produced nearly twice as much force at 100 s. Therefore, when contractile kinetics were modified independent of fatigue (e.g., cooling), optimizing the rate of activation to contractile speed demonstrated even greater fatigue resistance than the MVC condition. These data clearly indicate an advantage of adjusting muscle activation rate to optimize force output dependent on contractile speed.

Therefore, there was compelling evidence that despite the reduction in maximal MU firing rates during a sustained MVC optimal fusion is maintained due to peripheral contractile slowing and in turn, fatigue resistance is improved.

Is the muscle wisdom hypothesis still justified?

A primary limitation of the preceding fundamental studies (Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983) is that the stimulation rates used were higher than those observed during MVCs. For example, MU firing rates of the adductor pollicis during a non-fatiguing MVC are ~ 30 Hz (Bigland-Ritchie et al. 1983b, a). This is well below the high-frequency stimulation rates (e.g., 80 Hz) used by Jones, Bigland-Ritchie, Marsden, and colleagues. Therefore, it is unclear whether the increase in force maintenance when stimulation rates are lowered, which forms the basis of the muscle wisdom hypothesis, is a consequence of using artificially high activation frequencies.

It has been consistently reported in reduced preparation and humans that sustained muscle activation at artificially high stimulation rates causes impaired action potential propagation. This may occur at the neuromuscular junction (e.g., Brown and Burns 1949; Krnjević and Miledi 1958; Naess and Storm-Mathisen 1955) or within the muscle fibres themselves (e.g., Bigland-Ritchie et al. 1979; Jones et al. 1979; Lännergren and Westerblad 1986; Lüttgau 1965) or both. However, with cessation of high-frequency stimulation action potential propagation failure recovers rapidly in single frog muscle fibres (Lüttgau 1965; Lännergren and Westerblad 1986; Westerblad et al. 1990), whole cat muscle (Davis and Davis 1932) and individual MUs of small mammals (Clamann and Robinson 1985; Sandercock et al. 1985) and humans (Macefield et al. 1996). Indeed, when constant 80 Hz stimulation was reduced to 20 Hz the M-wave area rapidly recovered to near baseline values despite an ~ 70% reduction (Bigland-Ritchie et al. 1979). Therefore, a primary feature of the muscle wisdom hypothesis, in which reduction of activation frequency protects (Bigland-Ritchie et al. 1979; Jones et al. 1979) or delays (Marsden et al. 1983) against peripheral conduction failure, may be a consequence of artificially high rates of activation.

To explore these potential limitations Fuglevand and Keen, (2003) replicated in humans the studies by Jones and Bigland-Ritchie but electrical stimulation was performed with physiological rates. Ulnar nerve stimulation was done to stimulate the adductor pollicis and the highest frequency used was 30 Hz to match population recordings of MU firing rates during an MVC in this muscle (Bigland-Ritchie et al. 1983b, Bellemare et al. 1983).

Three 60 s trials were conducted: i) a sustained MVC; ii) progressively decreasing stimulation rate ('artificial wisdom') from 30–15 Hz (based on sustained MVC firing rates from Bigland-Ritchie et al. 1983b); iii) sustained 30 Hz stimulation rate (Fig. 8).

In accordance with Jones & Bigland-Ritchie (Bigland-Ritchie et al. 1979; Jones et al. 1979) the relative force loss during the progressively decreasing stimulation rate and the MVC condition were identical at ~ 40%. However, contrary to the previous reports the sustained high-frequency (i.e., 30 Hz) resulted in a significantly smaller ~ 20% loss of force. Therefore, decreasing the stimulation rate did not minimize force loss compared to a sustained high *physiological* frequency. In fact, the decreasing stimulation rate *enhanced* force loss and thus *decreased* fatigue resistance.

Similar to the findings of Bigland-Ritchie et al. (1979), the M-wave amplitude was not affected during the decreasing stimulation rate trial but was reduced in the constant 30 Hz trial after amplitude potentiation (for review McComas et al. 1993) during the initial 20 s. Immediately after the

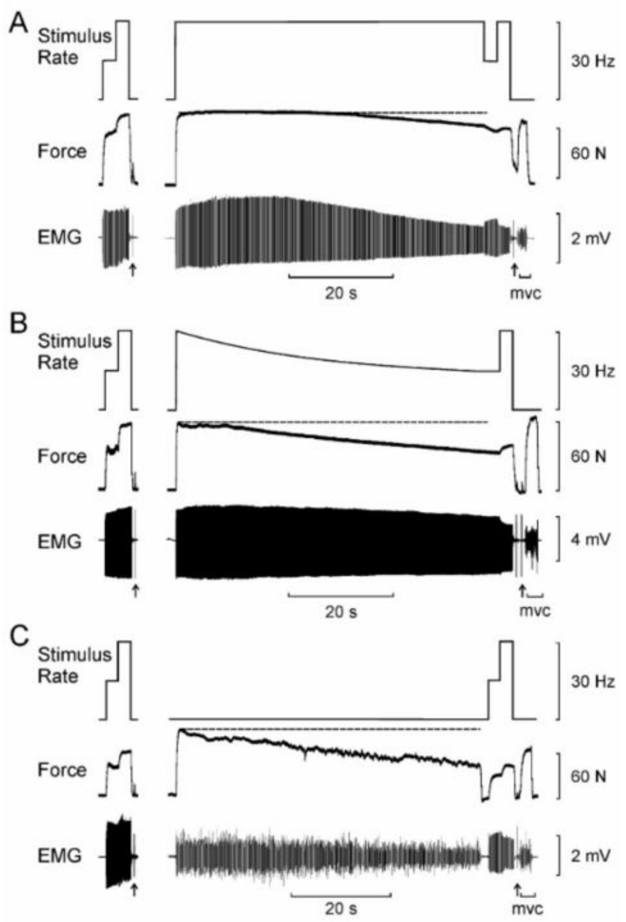

Fig. 8 Thumb adduction force (N) and electromyography (EMG, mV) of the adductor pollicis during **A** constant 30 Hz stimulation, **B** decaying stimulation rate from 30–15 Hz and **C** maximal voluntary contraction over 60 s of activation. Within each panel, there is the stimulation rate, force, and EMG tracings. Figure adapted from Fuglevand and Keen 2003 (reprinted with permission)

constant 30 Hz trial, stimulation at 15 Hz restored M-wave amplitude but did not improve force. Therefore, it seemed propagation impairment was not a contributing factor to force loss in this task. Additionally, the restoration of M-wave amplitude was immediately reversed when stimulation was increased back to 30 Hz.

Immediately after the decreasing stimulation rate trial (30–15 Hz), increasing stimulation to 30 Hz reduced M-wave amplitude by 19%. However, contrary to Jones and Bigland-Ritchie the increase in stimulation rate *increased* force by 22%. The prior studies (Bigland-Ritchie et al. 1979; Jones et al. 1979) showed no force increase at any point when switching to a high-frequency stimulation during the fatiguing task. Across all three trials, the M-wave peak-to-peak duration was similarly prolonged, which was likely due to slowed conduction velocity (e.g., Bigland-Ritchie et al. 1979; Juel 1988).

Fuglevand and Keen (2003), determined the reduced M-wave amplitude during 30 Hz simulation was due to signal cancellation of overlapping M-wave potentials (their Fig. 3). Importantly, this effect would become more pronounced throughout the contraction time course as M-wave duration prolongs (e.g., Bigland-Ritchie et al. 1979; Juel 1988; Fuglevand and Keen 2003). The cancellation may also explain the rapid recovery of M-wave responses following cessation of high-frequency stimulation (e.g., Bigland-Ritchie et al. 1979; Clamann and Robinson 1985).

The results from Fuglevand & Keen are in contrast to Jones & Bigland-Ritchie. The primary difference across studies was the stimulation rate employed. During the experiments of Jones & Bigland-Ritchie much less was known about maximal human MU firing rates and this was an acknowledged limitation of those original experiments (see Bigland-Ritchie 1981). However, to produce a force equal (or almost equal) to MVC artificially high rates (> 60 Hz) of stimulation were required by Jones & Bigland-Ritchie and Marsden and colleagues (Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983).

During sustained 30 Hz stimulation for 60 s there was a decline in M-wave amplitude by 30% (Fuglevand and Keen 2003), compared to 75% with sustained 80 Hz stimulation (Bigland-Ritchie et al. 1979). The differences between studies most likely are related to the different stimulation frequencies (Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983) or the number of pulses (Marsden et al. 1983). It is perhaps not surprising that the neuromuscular system is incapable of maintaining normal electrical propagation during excitation rates higher than physiological values, especially for a sustained duration (e.g., 60 s, Brown and Burns 1949; Naess and Storm-Mathisen 1955; Krnjević and Miledi 1958). Furthermore, differences could be related to the amount of signal cancellation which is a limitation of recording from extracellular surface electrodes (note above, for review see Fuglevand 1995). Indeed, MU firing rates may be > 150 Hz for a few intervals during rapid maximal contractions, however, these high rates apparently are not sustainable (Desmedt and Godaux 1977; Grimby et al. 1981a; Marsden et al. 1983; Van Cutsem et al. 1998).

A key finding by Fuglevand and Keen (2003) was that there was a dissociation between EMG decline and force loss. For example, after the decaying simulation rate condition (30 to15 Hz) the M-wave was not impaired. However, immediately following the task when the stimulation rate was increased to 30 Hz (from 15 Hz) force increased, despite a reduction in the M-wave amplitude. This dissociation is also likely related in part to the extent of signal cancellation. Therefore, a reduction in M-wave amplitude was not causative of force loss. Rather, despite some potential impairment in the M-wave amplitude, force loss was improved with high rates of stimulation.

If the reductions in M-wave amplitude are large enough the sarcolemma voltage-sensors and t-tubules will not completely engage, impairing activation for calcium release; thus, force loss will occur (Fuglevand 1995). However, the amplitude reduction (~30%) during the sustained 30 Hz stimulation may still operate within the excitation–contraction coupling safety factor and thus little or no activation failure occurs (Sandow 1952; Lännergren and Westerblad 1986). Conversely, the artificially high rates employed by Jones & Bigland-Ritchie may acutely overcome the safety factor, and thus impair normal excitation–contraction coupling, leading to force loss (Brown and Burns 1949; Sandow 1952; Naess and Storm-Mathisen 1955; Krnjević and Miledi 1958).

In the experiments by Jones & Bigland-Ritchie immediately following sustained artificially high stimulation rates of 80 Hz, stimulation at 20 Hz increased force and returned the M-wave to near baseline values. The adjustment to a physiological stimulation rate may have restored transmembrane concentration gradients, and thus both the M-wave and force were recovered. Therefore, it seems the primary reduction in force during the sustained artificially high-frequency stimulation was due to electrical transmission failure which surpassed the excitation–contraction coupling safety factor. However, during the high *physiological* stimulation rate there was some reduction in action potential propagation, although this reduction may be within the safety factor, but also could be a result of signal cancellation (Fuglevand and Keen 2003). Therefore, the conclusion that sustained high-frequency stimulation enhances force loss may be a consequence of the artificially high rates used by Jones and Bigland-Ritchie (1979) and Marsden et al. (1983). The use of high physiological rates (Fuglevand and Keen 2003) is a correct improvement on the original study design (Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983) and thus challenged the original conclusions.

When high physiological rates are sustained, force loss is minimized compared to both a sustained MVC or a progressive decline in stimulation rate. Progressively declining excitation rates (‘artificial wisdom’) clearly have a benefit in maintaining normal electrical transmission as the M-wave amplitude was not impaired (Bigland-Ritchie et al. 1979; Marsden et al. 1983), however, the impairments in electrical transmission when high *physiological* stimulation rates are sustained likely are not large enough to impair force output (Fuglevand and Keen 2003). Thus, the data from Fugelvand and Keen (2003) suggest the decline in maximal MU firing rates during a sustained MVC would contribute to, rather than preserve, force output. This did not support the muscle wisdom hypothesis but suggested force loss during sustained maximal activation is in part due to inadequate input from the central nervous system.

The data from Fuglevand and Keen (2003) provided insights and introduced major concerns regarding the original muscle wisdom proposal. This was concluded using physiological rates of stimulation, and this resolved a primary limitation of the work by Jones, Bigland-Ritchie, Marsden, and colleagues who used unphysiologically high rates (Bigland-Ritchie et al. 1979; Marsden et al. 1983). However, the high unphysiological rates were required to equal or near MVC force. Indeed, the physiological rate of 30 Hz used by Fuglevand and Keen produced only ~55% of MVC force which does not reflect the original hypothesis proposal, which was formulated on high-intensity (e.g., ≥75% MVC) or maximal contractions (Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983).

To resolve the discrepancy between studies Dudani et al. (2025) mimicked prior experiments (Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983; Fuglevand and Keen 2003) but employed a muscle group (dorsiflexors) that is capable of evoking high-intensity torque output (e.g., 80% MVC) in response to electrical stimulation at physiological rates of activation (Smith et al. 2014; Zero et al. 2023a). Therefore, by changing the muscle group the limitations from previous studies of unphysiological rates of activation and low force outputs was not a confounding factor. Three 60 s trials were conducted: i) a sustained MVC; ii) exponentially decaying stimulation rate (‘artificial wisdom’) from 40 to 20 Hz (based on sustained MVC firing rates from the tibialis anterior during dorsiflexion, Zero et al. 2023a); and iii) sustained 40 Hz stimulation rate.

Stimulation at 40 Hz produced ~82% MVC torque at pre-fatigue (baseline) values. The decaying rate of stimulation (i.e., 40–20 Hz) demonstrated less torque loss compared to the sustained high-frequency stimulation rate (i.e., 40 Hz) (Fig. 9). Furthermore, when the sustained high-frequency stimulation condition was switched to 20 Hz for 2 s at task termination (i.e., at 60 s) torque output was increased (~17%) (Fig. 9). Conversely, when the decaying stimulation was increased from 20 to 40 Hz for 2 s at task termination the torque loss was accelerated (~16%) (Fig. 9). Therefore, these recent data support the original experiments formulating the muscle wisdom hypothesis (Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983) and indicate declining rates of activation during high-intensity contractions are beneficial for the preservation of torque. Furthermore, these data indicate that during the initial 30 s the high-frequency and decaying rates of stimulation produced similar torque decline and only after 30 s of activation did the two conditions begin to deviate (Fig. 9). Therefore, it appears high physiological rates can be tolerated for a brief period, but that decaying rates become more beneficial as contraction duration progresses and the system is continually stressed.

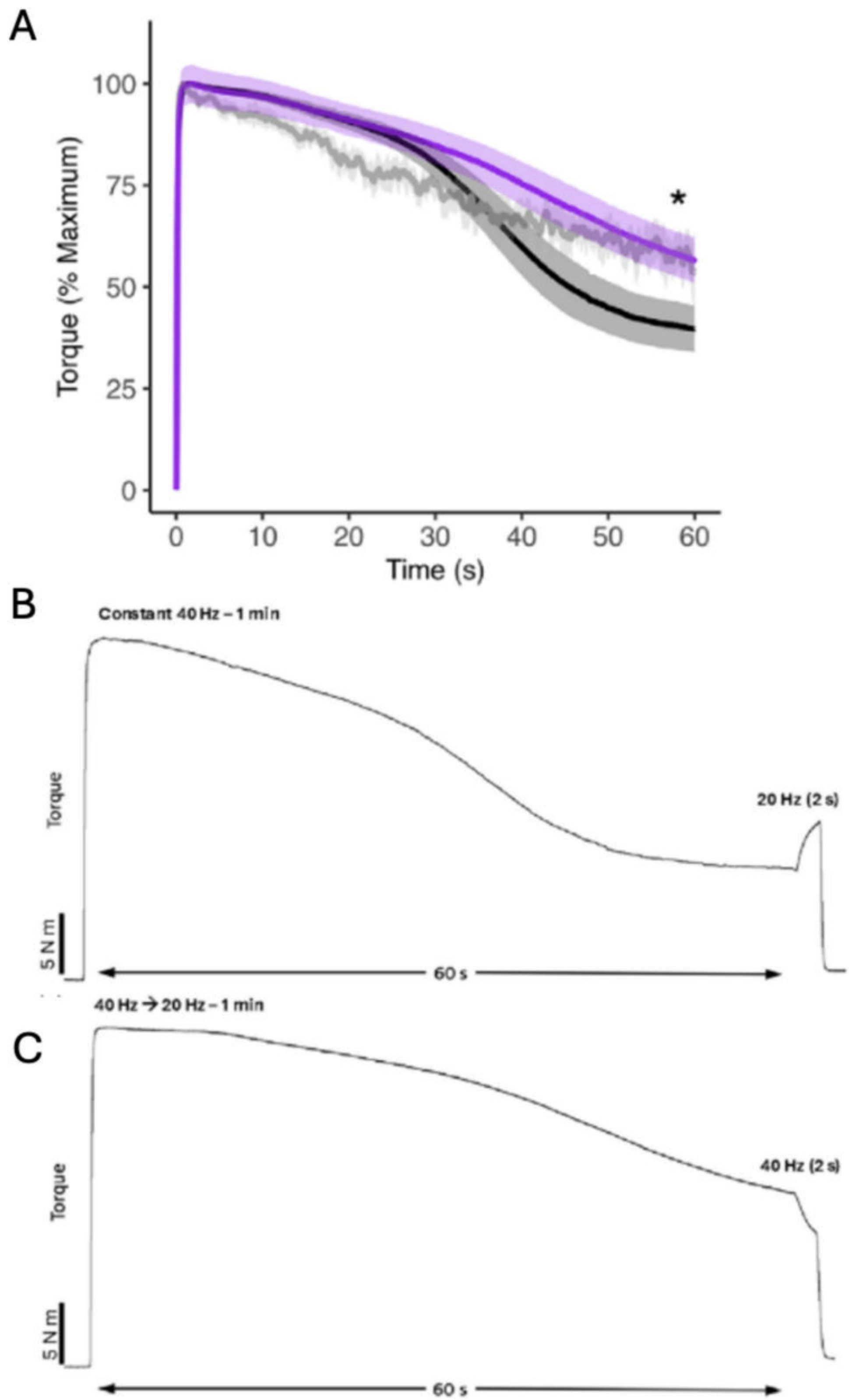

Fig. 9 **A** Mean dorsiflexion torque traces (as a percentage of maximum) for each fatigue condition. Purple, black and grey lines represent each fatigue condition which consists of decaying stimulation (40–20 Hz), sustained high-frequency stimulation (40 Hz) and maximal voluntary contraction conditions, respectively. Shaded regions represent the 95% confidence interval. *Indicates the decaying stimulation condition is significantly different than the sustained high-frequency stimulation and maximal voluntary contraction conditions. **B** and **C**: Exemplar dorsiflexion torque tracing (Nm) during stimulated contractions (**B**: sustained stimulation at 40 Hz and **C** decaying stimulation from 40–20 Hz). Note frequency change after 60 s of stimulation denoted in the figure. All stimulation was supramaximal over the fibular nerve. Figure from Dudani et al. 2025 (reprint permission not required as this article is distributed under the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited)

Immediately after all the fatiguing trials twitch responses were evoked with electrical stimulation (fibular nerve) and M-wave responses were recorded over the tibialis anterior (the primary dorsiflexor). Furthermore, in this experimental paradigm any reductions in the M-wave response are not likely due to signal cancellation because M-waves were recorded in response to a single electrical pulse while the muscle was at rest (immediately after the fatiguing task). For all trials twitch half-relaxation time slowed (> 30%), but M-wave amplitude was only reduced for the sustained 40 Hz stimulation condition (~ 23%). Therefore, as originally proposed, torque was preserved by reducing the activation rate during high-intensity contractions (e.g., ≥ 75% MVC) which maintained optimal activation by matching the fatigue-induced contractile slowing in combination with preserved peripheral electrical conductance. This recent study identified limitations of prior studies (Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983; Fuglevand and Keen 2003) resulting in support of the original muscle wisdom hypothesis.

During voluntary contraction single MUs fire asynchronously. This activation pattern maintains the muscles' series elasticity in a semi-stretched condition which achieves full tetanic tension at lower frequencies (Lind and Petrofsky 1978). During peripheral nerve stimulation MUs are synchronously activated, and thus often high unphysiological stimulation rates are required to achieve near-maximal force. Indeed, we support the statement by Gandevia (2001) that it is "unfortunate" there are so few nerve-muscle combinations that can be supramaximal stimulated to match maximal voluntary efforts. Therefore, in addition to the rate of activation, stimulation-induced contraction intensity (i.e., the task) is a critical variable for interpretations, as detailed below.

During a sustained MVC firing rates are presumed initially to be at maximum and thus rates can only be maintained or decline. Conversely, during a sustained submaximal contraction MUs do not initially fire at maximal rates and thus an increase in firing rate can occur to maintain the task demand. Indeed, to maintain submaximal force output (e.g., ≤ 50% MVC) MUs display diverse firing rate profiles as some may increase, decrease, or minimally change (Garland et al. 1994, 1997; Carpentier et al. 2001; Valenčič et al. 2024; Magnuson et al. 2024). Although diverse across single MUs, firing rates of newly recruited units (i.e., not recruited at the start of the task) are increased near the predefined 'task-failure' (Garland et al. 1997). Additionally, during sustained submaximal contractions the surface EMG signal increases throughout the contraction time course, which likely represents the recruitment of new MUs (Garland et al. 1997). It is interpreted that although the submaximal force target can still be maintained, higher firing rates, most common with newly recruited MUs, are required as the contractile capacity becomes impaired. Therefore, both increased firing rates and recruitment of previously inactivated MUs occurs to maintain submaximal force. These are key differences in MU behavior between sustained submaximal and maximal tasks. Indeed, it is appreciated that the rationale for the muscle wisdom hypothesis does not hold during submaximal fatiguing tasks (for review Garland and Gossen 2002).

As demonstrated, the response of firing rates is highly dependent on the task demand. Indeed, the muscle wisdom hypothesis was developed in relation to sustained MVCs. Based on observations of MU firing rates during sustained submaximal contractions it is not surprising the constant high-frequency stimulation condition had the lowest force loss in the experiments of Fuglevand and Keen (2003). This is because recruitment and rate coding of previously inactive MUs are key mechanisms to maintain submaximal force decline during sustained activation.

Electrical propagation of muscle during sustained maximal voluntary contractions

A key concept of the muscle wisdom hypothesis is that the reduction in maximal MU firing rates during a sustained MVC minimizes force loss by protecting against peripheral conduction failure. However, there is controversy as to whether electrical propagation is maintained during acute (≤ 60 s) MVCs, and thus it is unclear whether the observed reduction in maximal MU firing rates is indeed preventing peripheral propagation impairment as originally hypothesized.

Reduced preparations can provide mechanistic insights that are unavailable in an integrated neuromuscular system of the various factors that influence action potential propagation which are ultimately critical for interpretations of the muscle wisdom hypothesis. In these preparations activation induced impairments in action potential propagation can occur which are MU, fibre type, and species dependent (Hanson and Persson 1971; Bezanilla et al. 1972; Hanson 1974; Reinking et al. 1975; Clamann and Robinson 1985; Sandercock et al. 1985; Lännergren and Westerblad 1986, 1987; Metzger and Fitts 1986; Radicheva et al. 1986; Gardiner and Olha 1987; Enoka et al. 1989; Balog et al. 1994) but seem principally due to t-tubular impairments (Bezanilla et al. 1972; Lännergren and Westerblad 1986; Westerblad et al. 1990). Briefly, the "safety factor" (Sandow 1952) is smaller for fast-type mammalian fibres and thus they are more susceptible to impaired activation and subsequent impairments in force (for review see Fuglevand 1995).

To what extent the primary impairments of fast-type fibre propagation affect whole mixed human muscle electrical and contractile function is not clear. Furthermore, inferences of electrical propagation during voluntary contraction of human muscle are often from extracellular (surface) recordings, which likely do not reflect changes in t-tubules function. Others have diminished electrical propagation as a factor in fatigue and stating, "transmission fatigue and contraction fatigue appear as independent phenomena" (Steiman 1943) such that "under certain conditions muscles show variations in tension output which bear no fixed relation to the size of the action potential." (Sandow 1952) and "there is little evidence that HFF *(high-frequency fatigue)* is an important cause of fatigue in normal healthy muscle" (Jones 1996) or furthermore doubt as to whether it "actually occurs during voluntary contractions" (C.M. Wiles, post presentation discussion p.g. 193 in Human Muscle Fatigue: Physiological Mechanisms, 1981). To address these discrepancies the significance of electrical propagation during fatigue of voluntary human contractions will be reviewed.

In studies of fatigue, the M-wave has been utilized as a measurement of peripheral conduction. However, "the events that occur at the muscle fiber membrane are not always reflected accurately by M-waves recorded from the muscle surface" (Bigland-Ritchie et al. 1995). Therefore, many considerations are required to extrapolate the findings from reduced preparations to sustained voluntary contractions in humans.

During a sustained ≥ 45 s MVC there have been reports of increases, decreases or no change in various M-wave assessments (Merton 1954; Stephens and Taylor 1972; Bigland-Ritchie et al. 1979, 1982, 1983a; Kukulka and Peter Clamann 1981; Merton et al. 1981; Kranz et al. 1983; Marsden et al. 1983; Woods et al. 1987; Bellemare and Garzaniti 1988; Thomas et al. 1989; Fuglevand and Keen 2003; Rodriguez-Falces and Place 2017). It is important to summarize these experiments critically, which have been performed by separate lab groups employing different methodologies and tested muscle groups. These findings have helped elucidate whether the expected firing rate reduction during sustained MVCs is a mitigating factor, with a concurrent delay of electrical propagation impairments, as originally proposed. The original findings by Merton indicating no change in M-wave amplitude during sustained MVCs (> 1 min) (Merton 1954) since have been corroborated (Bigland-Ritchie et al. 1979, 1982, 1983a; Merton et al. 1981). This suggested no impairments in electrical transmission despite significant reductions in force. Stephens and Taylor (1972) challenged these findings using the first dorsal interosseous muscle. During sustained MVCs, they reported a reduction in the M-wave amplitude of the first phase, and additionally the M-wave area (assessed using a fixed time interval) decreased. Contrary to Merton, (Merton 1954; Merton et al. 1981) and Bigland-Ritchie (Bigland-Ritchie et al. 1979, 1982, 1983a), the authors suggested impaired neuromuscular transmission contributed to force loss.

Using the adductor pollicis Bigland-Ritchie and colleagues consistently reported no reductions in M-wave amplitude during sustained MVCs (Bigland-Ritchie et al. 1979, 1982, 1983a; Bigland-Ritchie 1981). A common criticism of assessing M-waves with hand muscles is the close proximity of other muscles sharing the same nerve supply. Thus, during fatiguing contractions, M-wave responses may be contaminated from non-fatigued muscles within the recording area of the electrodes (e.g., Zijdewind and Kernell 1994). This may partly explain diverse findings even within the same lab groups (cf. Marsden et al. 1983; Merton 1954; Merton et al. 1981). These criticisms were systematically addressed by Bigland-Ritchie et al. (1982). For the fatiguing task, there was simultaneous maximal effort > 60 s co-contraction of first finger abduction and thumb adduction. Therefore, if there is any contamination of the M-wave (recorded over the first dorsal interosseous and adductor pollicis) the closest muscle in proximity would also be fatigued. Using co-contraction, no changes in M-wave peak-to-peak amplitude were reported, despite a 30–50% reduction in force. However, the duration of the waveform was increased, and thus because no changes in amplitude were observed the total and half waveform areas increased. Furthermore, similar responses were observed using intramuscular EMG in both muscles which would also limit concerns of M-wave contamination (Bigland-Ritchie 1981; Woods et al. 1987). Therefore, the maintenance of M-wave amplitude shown in the adductor pollicis muscle during sustained MVCs (Merton 1954; Bigland-Ritchie et al. 1979; Bigland-Ritchie 1981) was likely not due to contamination from unfatigued ulnar innervated muscles.

A major difference between Bigland-Ritchie and colleagues (Bigland-Ritchie et al. 1979, 1982, 1983a; Bigland-Ritchie 1981; Woods et al. 1987; Thomas et al. 1989) and Stephens and Taylor (1972) were that the latter assessed the M-wave area over a fixed time interval. It has been consistently shown that the M-wave duration can increase during sustained activation from slowed conduction velocity (Juel 1988). Therefore, the fixed time interval would encompass a smaller portion of the total waveform (Bigland-Ritchie et al. 1982). Indeed, when the same analysis was employed by Bigland-Ritchie a decline in the area was observed (Bigland-Ritchie et al. 1979, 1982) similar to Stephens and Taylor (1972). Therefore, this difference in analysis clearly explains the differences in M-wave area reported across studies.

Maintaining supramaximal stimulation with optimal electrode positioning over the peripheral nerve is critical for assessing the M-wave response. During sustained MVCs, Bigland-Ritchie et al.(1982) reported instances of declining M-wave amplitude recorded over the first dorsal interosseous (FDI) muscle. However, the amplitude could always be restored by repositioning the stimulating electrode, and this effect has also been reported with fibular nerve stimulation for tibialis anterior M-wave assessment (Thomas et al. 1989). Therefore, reports of M-wave amplitude reduction may be an artifact of suboptimal electrode positioning and could explain some discrepancies across studies (Thomas et al. 1995).

Bellemare and Garzaniti (1988) reported conflicting results to Bigland-Ritchie & colleagues (e.g.,Bigland-Ritchie et al. 1982) using the adductor pollicis. During a 90 s MVC, the first phase amplitude of the M-wave declined. However, M-wave area and duration were not reported. Furthermore, additional M-waves were recorded from the abductor digiti minimi which is ulnar innervated but does not contribute to thumb adduction. Therefore, suboptimal stimulating electrode position could not be the cause of the declining M-waves because abductor digiti minimi responses were well maintained.

Bellemare and Garzaniti (1988) suggested the difference between their work and Stephens and Taylor (1972) compared to the work showing no impairment in M-wave amplitude (e.g., Bigland-Ritchie et al. 1982) was the used of paired (Stephens and Taylor 1972) or brief tetanic stimulation (Bellemare and Garzaniti 1988) versus a single impulse (e.g., Bigland-Ritchie et al. 1982) to assess M-waves. It was thought using paired stimuli the initial impulse would produce an antidromic volley which would collide with descending voluntary inputs. Thus, the subsequent impulse(s) would not be interfered with voluntary activity and provide a pure M-wave response. However, acknowledging this difference between studies Bigland-Ritchie et al. (1982) reported "no consistent difference" using paired impulses compared to a single pulse. Therefore, it seems unlikely this methodological difference contributed to the dissimilar results.

A potential discrepancy among the studies is the 'baseline' values being compared. As acknowledged by both groups (Bigland-Ritchie et al. 1982; Bellemare and Garzaniti 1988; Thomas et al. 1989) M-waves superimposed on an MVC can differ in shape and amplitude compared to those evoked in a relaxed muscle. To account for these differences, which are likely unrelated to genuine alterations in electrical propagation, Bigland-Ritchie and colleagues compared the M-waves reported during a sustained (e.g., 60 s) MVC to the M-wave during a brief non-fatiguing 3–5 s control MVC. Conversely, other reports compared the M-waves obtained during sustained MVCs to a relaxed muscle (e.g., Bellemare and Garzaniti 1988) and observed immediate reductions in M-wave amplitude during a fatiguing task.

It has been shown that changes in muscle architecture alter the M-wave response. Specifically, the M-wave duration decreases as force increases (Linnamo et al. 2001) and simulation studies suggest fibre shortening enhances the 2nd phase amplitude and decreases duration (Rodriguez-Falces and Place 2014). Indeed, this has been corroborated experimentally as the M-wave 2nd phase amplitude increased and duration decreased when comparing responses evoked over contractions at 20 and 80% MVC (Rodriguez-Falces and Place 2015). Therefore, contraction-induced architectural alterations can affect the M-wave response which are unrelated to fatigue or changes in peripheral conductivity. In addition, these more recent insights may explain much of the discrepancy in findings among studies.

If a genuine decline in the M-wave occurs during a sustained MVC the most pertinent question is whether this reduction is evidence of insufficient muscle activation, and thus a contributor to force loss. During a 5 min dorsiflexion, MVC Thomas et al. (1989) found no reduction in tibialis anterior M-wave amplitude but an increase in duration and thus also area. However, during a 5 min finger abduction MVC the FDI M-wave amplitude declined ~ 25%. Furthermore, duration was prolonged ~ 30% and thus the total M-wave area was largely unaffected. Thus, within the same participants during the same fatiguing task the response of M-waves can be muscle dependent. However, in the FDI muscle, the reduction in M-wave amplitude (~ 25%) was not comparable to the ~ 70% reduction in force. Indeed, the reduction in M-wave amplitude occurred over the first 2 min and afterwards no further reduction was observed despite significant force loss during the final 3 min. Therefore, there is a dissociation between M-wave amplitude reduction and force loss (also see Clamann and Robinson 1985; Kernell et al. 1987; Sandercock et al. 1985). Furthermore, single pulse supramaximal nerve stimulation did not enhance force during the first 2 min of the MVC (during M-wave amplitude reduction) suggesting maximal muscle activation was maintained.

During a 5 min finger abduction MVC, the reduction in amplitude coincided with the FDI M-wave response becoming less synchronous and separating into two peaks (Thomas et al. 1989). A greater dispersion may have occurred due to uneven slowing of conduction velocity across muscle fibre and MU types and thus contributed to the lower M-wave amplitude (Thomas et al. 1989). As noted above (Fuglevand 1995), fast-type fibres would have a lower safety factor and thus are more susceptible to electrical propagation impairment (Hanson 1974; Sieck and Prakash 1995). Additionally, larger MUs (likely composed of a greater % of fast-type fibres) are more prominent superficially (Lexell et al. 1983; Knight and Kamen 2005). Surface detected potentials are preferentially influenced by the closest (more superficial) MUs relative to the recording electrodes (Fuglevand et al. 1993a; Merletti et al. 2008). Therefore, any modifications to the peripheral conductance of large superficial MUs would greatly affect the surface-detected M-wave response. For example, using a MU population (120 units) to simulate a hand muscle, not activating the eight largest MUs caused a ~ 25% decrease in M-wave amplitude. Conversely, the removal of the smallest 60 MUs only caused a ~ 6% reduction in amplitude (Keenan et al. 2006). Therefore, although the M-wave represents a synchronous activation of all MUs in response to a supramaximal stimulus, the surface-detected response is differently affected by individual MUs. This limitation must be appreciated when assessing M-waves during fatiguing contractions.

Unfortunately, it seems differences in methodologies and analysis, suboptimal stimulation position, cross contamination or the muscle tested may account for the heterogeneity of M-wave responses during sustained (≥ 45 s) MVCs. However, based on the works summarized, if a genuine reduction in electrical propagation occurs during sustained MVCs it seems unlikely to account for much of the force loss in this task. Furthermore, when reductions in the M-wave amplitude are reported during sustained MVCs the reduction is much less than sustained stimulation at high, often unphysiological frequencies in various experimental models (e.g., Bigland-Ritchie et al. 1979; Jones 1996). Therefore, it seems likely, as the original muscle wisdom hypothesis proposed, that the reduction in maximal firing rates during sustained MVCs limits or delays electrical propagation failure and consequently maintains function within the safety factor (Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983).

A central question remaining regarding the muscle wisdom hypothesis, and not easily addressed is “to what extent failure of electrical propagation would occur in voluntary contractions if the motor neuron discharge rates did not change.” (Bigland-Ritchie 1981). Here the focus of electrical propagation was with reference to acute sustained MVCs, however, propagation disturbances may occur with other fatiguing tasks (e.g., Fuglevand et al. 1993b; Marsden et al. 1983) and indeed, as noted by others “it would be surprising if impaired transmission does not occur during fatigue from some types of exercise since safety margins seldom exceed those sometimes called upon in one task or another” (Bigland-Ritchie et al. 1995).

Reconsidering the justification for the muscle wisdom hypothesis

The muscle wisdom hypothesis suggests that the reduction of maximal MU firing rates would maintain optimal muscle activation because of slowing contractile speed (Marsden et al. 1971; Bigland-Ritchie and Woods 1984). Thus, lower rates of activation would be adequate to maintain a fully fused tetanus and therefore reduced voluntary firing rates would be an economical and functional response (Bigland-Ritchie 1981; Marsden et al. 1983; Bigland-Ritchie and Woods 1984). Indeed, results were interpreted that “to obtain the most prolonged and powerful voluntary contractions the rate of discharge of motor impulses should slow down consistent with maintaining a fully fused tetanus as the contraction proceeds” (Marsden et al. 1976).

Fatigue-induced changes to the stimulated force-frequency relationship

The primary assumption to support this hypothesis is that the electrically stimulated force-frequency relationship shifts leftward as contractile speed slows with fatigue (Fig. 7, e.g., Bigland-Ritchie et al. 1983a, b; Bigland-Ritchie and Woods 1984). However, this is not universally reported (Fig. 10). Specifically, when electrically stimulated force-frequency relationships are normalized to the highest frequency used (e.g., 100 Hz) there is a rightward shift at low and moderate frequencies in single human MUs (Fuglevand et al. 1999) and whole muscle (Jones et al. 1989; Binder-Macleod and McDermond 1992; Binder-Macleod et al. 1998; Meyers et al. 2001). Furthermore, the rightward shift is maintained when the relationship is plotted in absolute values, however, the plateau portion of the relationship is lowered with fatigue (Binder-Macleod and McDermond 1992 their Fig. 2). Indeed, when plotted with absolute values the frequencies required to evoke a maximal response are not altered following fatiguing activation (Binder-Macleod and McDermond 1992). Therefore, the same frequency is required for a maximal response during fatigue compared to a baseline state, which is contrary to what was originally suggested (e.g., Bigland-Ritchie 1993; Bigland-Ritchie and Woods 1984, Fig. 7). Thus, a leftward shift in the force-frequency relationship is not an obligatory response to muscle fatigue. If a rightward shift does occur this would suggest the reduction in maximal firing rates during a sustained MVC does contribute to force loss as inadequate activation occurs.

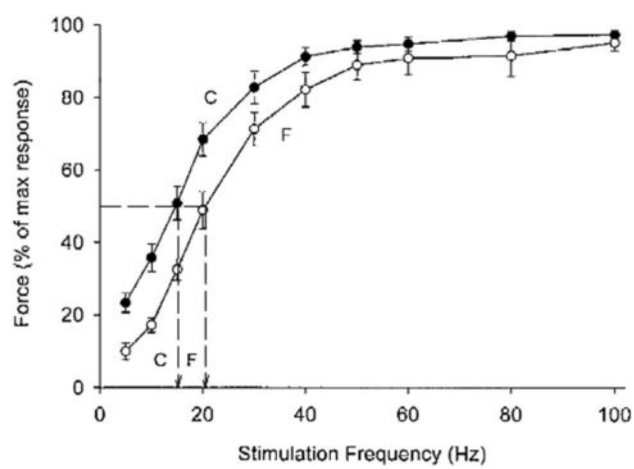

Fig. 10 Electrically evoked force-frequency relationships of the quadriceps pre- (control) and post- a fatiguing task. Force normalized to maximal evoked response and frequency of stimulation (Hz) denoted on x-axis. Control (C) and fatigue (F) denoted by closed and open circles. Dashed line indicates the frequency required to evoke 50% of the maximal response in each condition. Data are presented as mean ± standard error. Figure adapted from Meyers et al. 2001 (reprinted with permission)

Although alterations in contractile speed greatly modify force summation on their own, it is the relationship between changes in speed *and* force-generating capacity that inevitably modify summation during or following fatiguing contractions. Therefore, whether summation is improved (i.e., leftward shift) or impaired (i.e., rightward shift) is dependent on the fatiguing task. For example, Bigland-Ritchie and colleagues (Bigland-Ritchie et al. 1983) showed immediately after a 60 s MVC the ratio between sub-tetanic (7 Hz) and tetanic stimulation (50 Hz) was greatly improved due to slowed contractile speed (Fig. 7, Bigland-Ritchie et al. 1983a; Bigland-Ritchie and Woods 1984). Although a range of frequencies was not employed to create a complete force-frequency graph, these findings would suggest a leftward shift of the relationship (e.g., Davis and Davis 1932). Therefore, with a 60 s MVC task it seems likely a leftward shift occurs (Bigland-Ritchie et al. 1983a). Indeed, reports indicating a rightward shift after a fatiguing task were varied including submaximal and intermittent contractions (Jones et al. 1989; Binder-Macleod and McDermond 1992; Fuglevand et al. 1999). This is important as the muscle wisdom hypothesis was established with sustained MVCs and mechanisms of force loss are task-dependent (Bigland-Ritchie et al. 1995), and, furthermore, the activation history of the muscle will greatly influence the force-frequency relationship (Binder-Macleod and Clamann 1989).

Do motor unit firing rates consistently match contractile speed?

As highlighted earlier, motoneuron input seems well matched to contractile speed across various preparations (Burke 1981; Kernell 1995; Macefield et al. 1996; Gossen et al. 2003). Bigland-Ritchie and colleagues sought to explore whether changes in contractile speed could modify maximal MU firing rates in the absence of fatigue (force loss). This was done through alterations in joint angle (muscle length) and muscle temperature (Bigland-Ritchie et al. 1992a, b).

When muscles are placed in a shortened position, electrically evoked isometric contractile properties are faster and thus greater rates of stimulation are required for fusion to occur (Rack and Westbury 1969; Gandevia and Mckenzie 1988). When the ankle was dorsiflexed 15° from neural (90°) twitch contraction duration and half-relaxation time were 11 and 18% faster. However, despite the differences in contractile speed there was no difference in maximal tibialis anterior MU firing rates (Bigland-Ritchie et al. 1992a).

In a separate experiment, cooling the muscle (first dorsal interosseous) by ~ 5 °C was used to match the slowing contractile rates observed following the 60 s sustained MVC. During the sustained MVC, MU firing rates declined ~ 50% as expected. However, despite slowing contractile speed by cooling the muscle there was no effect on maximal MU firing rates (Bigland-Ritchie et al. 1992b; see also Marsden et al. 1983). Thus, collectively when twitch contractile speed was slowed independent of fatigue, firing rates were not modified, thereby diminishing a potential causative relation between these two factors. Therefore, based on these separate experiments it was suggested that the reduction of firing rates during sustained maximal activation was not triggered by mechanical adaptations of the muscle per se (Bigland-Ritchie et al. 1992a; Bigland-Ritchie et al. 1992b). However, it does appear the fatigue-induced changes in the muscle (e.g., elevated H^+), which slow contractile speed, reduces firing rates (Bigland-Ritchie et al. 1986). Therefore, it is reasonable to conjecture that the mechanism of contractile slowing must be due to fatigue-induced changes in the muscle for the occurrence of firing rate reduction.

Nonlinear history-dependent properties of muscle

Muscle properties unrelated to contractile slowing could also explain the maintenance of force despite declining MU firing rates. This includes factors such as catch-like properties (Bevan et al. 1992; Laouris and Stuart 1993; Binder-Macleod and Kesar 2005), nonlinear force summation (Brown and Matthews 1960; Demieville and Partridge 1980; Parmiggiani and Stein 1981; Clamann and Schelhorn 1988; Powers and Binder 1991) and twitch potentiation (Burke et al. 1973; Duchateau and Hainaut 1986; Rassier and MacIntosh 2000). Rates of activation are often higher (e.g., > 100 Hz) at contraction onset (Desmedt and Godaux 1977; Grimby et al. 1981a; Marsden et al. 1983) for a few impulses before declining. This decline is not related to fatigue per se, but rather once initial fusion is obtained high rates are not required to maintain force due to intrinsic features of the muscle–tendon unit which collectively cause a hysteresis effect of the stimulated force-frequency relationship (Clamann 1970; Gibson et al. 1988; Binder-Macleod and Clamann 1989; Macefield et al. 1996). These effects would be most prominent during sustained isometric contraction as once the series elastic slack is tightened during the initial rate of force development force maintenance would require lower rates of activation. Thus, intrinsic mechanical features of skeletal muscle may in part explain the maintenance of force despite declining rates during sustained activation, independent of contractile slowing.

Fused and maximal contractions are not equivalent

A strong rational for matching the reduction of firing rates to slowing contractile speed is that any rate above what is necessary for complete fusion would be "uneconomical" (Bigland-Ritchie 1981) and provide "no effective return in a higher contraction tension"(Eccles et al. 1958). However, the stimulation rate to induce a completely fused contraction is lower than the rate required for maximal force production. Thus, maximal, and fused are not equivalent or interchangeable terms (Kernell 1995). Indeed, with stimulation of single human MUs complete fusion can occur before maximal force output (Macefield et al. 1996). Thus, the degree of fusion cannot fully account for force (Macefield et al. 1996). Therefore, the concept that reduced firing rates maintain maximal force because *fusion* is maintained is not upheld (Marsden et al. 1971; Bigland-Ritchie 1981; Bigland-Ritchie and Woods 1984).

Additional mechanisms for counteracting electrical propagation impairment

In addition to the decline of MU firing rates during a sustained MVC several "sophisticated" (Jones 1996) mechanisms exist to counteract or minimize electrical propagation failure. For example, the impairment in electrical propagation due to the rise of extracellular K^+ with repetitive muscle excitation can be partly compensated by electrogenic Na^+-K^+-ATPase pump activation (Hicks and McComas 1989; Hicks et al. 1989; McComas et al. 1993; Fowles et al. 2002; Fraser et al. 2002; McKenna et al. 2008) and the production of lactate (Pedersen et al. 2005; De Paoli et al. 2010). Therefore, several factors may concurrently work with the reduction of maximal MU firing rates to minimize electrical propagation failure to ensure adequate activation of the contractile machinery.

Considerations of the muscle wisdom hypothesis

A primary limitation of the muscle wisdom hypothesis is correlating whole muscle contractile properties to the firing rate of single MUs. It is well appreciated that human MUs display diverse contractile capacity (for review see Bigland-Ritchie et al. 1998). For example, using spike-triggered averaging during dorsiflexion, tibialis anterior MUs had torque outputs from 0.7—171 mN·m (Van Cutsem et al. 1997). Extreme ranges were also reported using an alternative approach of single motor axon stimulation, in which maximal MU toe extensor output ranged from 29.9–188.1 mN (Macefield et al. 1996). Indeed, similar diversity was also observed in muscles of the human hand (Thomas et al. 1991b, a; Fuglevand et al. 1999).

Motor unit heterogeneity in response to sustained electrical stimulation

The heterogeneity of MU output is also evident in response to fatiguing contractions (Clamann and Robinson 1985; Sandercock et al. 1985; Gordon et al. 1990; Sargeant and Jones 1995). Indeed, differences in fatigability are an important characteristic for the classification of MU types and in response to a standard fatigue test MUs of the cat can display a > 10-fold difference in force loss (Burke et al. 1973; Burke 1981). Extreme ranges in fatigue are also evident with single human MUs during single motor axon stimulation (e.g., Bigland-Ritchie et al. 1998). These differences are important to acknowledge as mechanisms contributing to force loss are dependent on the MU type (Clamann and Robinson 1985). Specifically, through stimulation of single MUs in the cat it was concluded type S MUs display "electrical fatigue" compared to FF units which was almost entirely "mechanical fatigue", subsequently type FR units displayed both (H.P. Clamman post-presentation discussion p.g. 152 *Human Muscle Fatigue: Physiological Mechanisms,* 1981, see also Clamann and Robinson 1985). This distinction between MU types is critical as an aspect of the muscle wisdom hypothesis is that the reduced firing rates will delay electrical propagation failure. Thus, the relative effectiveness of reducing firing rates to delay electrical propagation failure will vary depending on the MU type. This was a recognized limitation of the experiments which led to the muscle wisdom hypothesis as "the relative benefit from changing motor neuron firing frequency may depend on differences between the electrical and mechanical properties of each unit type" (Bigland-Ritchie 1981) and that "(*whole*) muscle fatigue is thus the aggregate of motor unit fatigue" (H.P. Clamman post-presentation discussion p.g. 148 in *Human Muscle Fatigue: Physiological Mechanisms*, 1981). However, the features of individual motor units would not be captured with whole-muscle electrical stimulation (e.g., Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983).

The matching of contractile speed and firing rates is also important to distinguish between MU types. In response to fatiguing stimulation, individual single human MUs display a diverse response as force can be severely depressed or minimally effected; additionally, contractile rates (i.e., speed) can increase, decrease, or not change (Thomas et al. 1991b). Furthermore, in cat MUs these differences seem to be stratified by MU type. Specifically, during a fatigue test twitch contraction duration decreased (i.e., faster) for type S units but increased (i.e., slower) for type FF (Dubose et al. 1987). Therefore, contractile slowing is not an obligatory response to fatigue and the concept of matching firing rates to contractile speed would be dependent on the MU type. Furthermore, the assessment of whole muscle contractile output with electrical stimulation would not capture differences in individual MUs.

Motor unit heterogeneity in response to sustained maximal voluntary contraction

Following the activity of the same MU across a sustained MVC is technically very challenging. Indeed, much of our understanding of maximal firing rates is from population MU sampling from monopolar electrodes (e.g., Bellemare et al. 1983). However, Grimby and colleagues (Grimby et al. 1981a) were successful and published a series of experiments (Grimby and Hannerz 1977; Borg et al. 1978; Grimby et al. 1979, 1981b; Hannerz and Grimby 1979). The discrimination of discrete single MU trains from the tibialis anterior and short toe extensor of the hallux was possible because MU numbers were reduced after several months of lesions to terminal nerve twigs and muscle fibres. Furthermore, in participants with an accessory deep peroneal nerve the main deep peroneal nerve was blocked with lidocaine, thus only a few MUs were active.

Although MU types could not be identified, units were grouped based on conduction velocity and twitch contraction duration. The MUs with a conduction velocity > 45 m/s and a contraction duration < 50 ms generally had higher recruitment thresholds (here after defined as high threshold MUs) compared to MUs with a conduction velocity < 40 ms and contraction durations > 60 ms (here after low threshold MUs). The high threshold MUs had maximal firing rates of ~ 50 Hz and minimum rates of above 20 Hz. Conversely, the lower threshold MUs had maximal rates of 30 Hz and a minimum rate below 10 Hz.

During sustained MVCs, all MUs declined but the reduction was varied. The decline in firing rate was more rapid for higher threshold MUs with initially higher rates (see also Marsden et al. 1983). Furthermore, when these MUs dropped to their minimum rate they began to fire in a phasic manner throughout the contraction. This cessation of MU firing during sustained MVCs has been corroborated elsewhere (Marsden et al. 1983; Peters and Fuglevand 1999). Conversely, lower threshold MUs with a lower initial firing rate could maintain rates at 15–20 Hz and continued to fire tonically. Indeed, muscle fibres of these units continued to show complete fusion despite the lowering rates. The authors proposed muscle fibres of higher threshold MUs are protected from severe fatigue through a central mechanism to induce phasic firing and mitigate peripheral excitation failure (Grimby et al. 1981b). This is supported by in vitro and in situ experiments in the rat, stating "intermittent presynaptic failure of propagation tends to protect the muscle fibre from excessive stimulation and to permit a fatigued muscle fibre to resume activity at a lower frequency" (Krnjević and Miledi 1958). If this type of mechanism exists it would be advantageous in maintaining electrical propagation specifically for fast-type muscle units (Hanson 1974). The variability of single MU responses is clear; however, it would seem unlikely the mechanisms for firing rate reduction, due to some combinations of altered sensory (afferent) feedback (Bigland-Ritchie et al. 1986; Bongiovanni and Hagbarth 1990; Gandevia et al. 1990; Macefield et al. 1993), intrinsic (biophysical) motoneuron adaptations (Kernell and Monster 1982a, b) and alterations in descending drive (Gandevia et al. 1996; Taylor et al. 1996), could regulate a unique and tailored control at the single MU level to maintain optimal contractile output (see Gandevia 2001; Stuart and Callister 1993).

Electrical stimulation does not represent voluntary contraction

Although electrical stimulation is a useful tool to assess contractile function (Maffiuletti et al. 2023), there are several limitations when making inferences about voluntary contractions. Indeed, at a Neuromuscular Fatigue symposium as a group (> 50 participants) it was recommended "that one should, in fatigue studies, be cautious when using results from electrically induced contractions to interpret fatigue of voluntary contractions… muscle usage is likely to be markedly different in these two situations" (In *Neuromuscular Fatigue* p.g. 193, e.d. A.J. Sargeant and D. Kernell 1993). These limitations are important to consider as the primary data to indicate a reduction in activation rate preserves, rather than contributing to force loss comes from electrically stimulated contractions (Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983).

During supramaximal electrical stimulation, MUs are activated synchronously. Therefore, when the stimulated rate is modified (e.g., 'artificial wisdom') all MUs are similarly activated. It is well established that there is an inherent firing rate variability of MUs (Clamann 1969), and thus synchronous activation of all MUs does not occur under voluntary contraction. Indeed, synchronous activation does not take advantage of the series elasticity of the system in a similar manner as asynchronous activation (Rack and Westbury 1969). Additionally, maximal firing rates of individual MUs within the same muscle can differ threefold (e.g., Connelly et al. 1999; Grimby et al. 1981a, b) and as noted above the decline in rates are variable among MUs (Grimby et al. 1981a; Marsden et al. 1983). Therefore, compared to a sustained MVC, individual MUs may have been activated more, or less often than when artificially stimulated to induce fatigue. Furthermore, when a standard stimulation rate is employed to fatigue single MUs of humans or the cat there is a wide range of force loss and often opposing changes in contractile speed (Burke et al. 1973; Burke 1981; Clamann and Robinson 1985; Sandercock et al. 1985; Thomas et al. 1991b; Fuglevand et al. 1999). Synchronous electrical stimulation would also disregard the potential of firing cessation that may also occur in some MUs (Grimby et al. 1981a; Marsden et al. 1983; Peters and Fuglevand 1999). Thus, despite the discrepancy between single MUs, electrical stimulation artificially induces synchronous activity. These factors must be considered when making inferences from stimulated to voluntary contractions.

Furthermore, in most muscle groups electrical stimulation cannot induce near MVC force with physiological rates of activation. Rather, high unphysiological rates are required (e.g., Jones et al. 1979; Marsden et al. 1983), and as noted above (see section 'Electrical propagation of muscle during sustained maximal voluntary contractions') this may induce an artificial ('high-frequency') fatigue (Jones 1996) response limiting interpretation of results to voluntary contractions. Despite the limitations noted above, the use of electrical stimulation was vital to the formation of the muscular wisdom hypothesis with the primary benefit being that the rate of stimulation can be controlled and thus the effect of activation rate can be investigated systematically.

Is the decline in motor unit firing rates during maximal contractions an invariable consequence?

The reduction in MU firing rates during a sustained (e.g., > 30 s) MVC has been replicated in several upper and lower limb muscles (Grimby et al. 1981a, b; Bigland-Ritchie et al. 1983a, 1986; Marsden et al. 1983). However, during sustained dorsiflexion MVCs of the big toe (60–180 s) firing rates of the extensor hallucis longus did not decline (Macefield et al. 2000). Therefore, firing rate reduction is not an invariable response to sustained MVCs. Those authors suggested the extensor hallucis longus shows minimal adaptations as it is comprised of predominantly fatigue resistant slow type MUs (Macefield et al. 2000). However, this explanation is not complete because for example the tibialis anterior which is supplied by the same common nerve and is also predominantly slow type (Johnson et al. 1973) displays declining rates during sustained MVCs (Grimby et al. 1981a; Rubinstein and Kamen 2005; Zero et al. 2023a). Indeed, the soleus which is 85% slow type fibres (Johnson et al. 1973) with unusually low maximal firing rates (Bellemare et al. 1983), also demonstrates a reduction in firing rates during sustained high-intensity (75% MVC) contractions (Dalton et al. 2010). Future studies should systematically explore this discrepancy of the extensor hallucis longus.

Contraction duration

Contraction duration is an important concept to consider when evaluating the muscle wisdom hypothesis. Prior to any fatiguing stimulus it is well known that low frequencies of activation (e.g., 20 Hz) produce weaker contractions compared to high frequencies (e.g., 80 Hz). Conversely, with continuous fatiguing activation lower frequencies begin to produce greater forces (Figs. 1 and 9). However, when comparing across studies and preparations, this does not instantaneously occur, and the lower rates only begin to produce greater force than high frequencies as contraction duration is prolonged and fatiguing influences continually develop (Figs. 1 and 9). Presumably, several factors are involved but likely fatigue-induced alterations in ionic conductance (Jones et al. 1979), electrical propagation (Bigland-Ritchie et al. 1979) and contractile kinetics (Bigland-Ritchie 1981; Marsden et al. 1983) must occur before the lowered rates become optimal for muscle excitation.

Is the muscle wisdom hypothesis a case of coincidence?

There is a strong relationship between contractile slowing and the reduction in MU firing rates during sustained MVCs (Bigland-Ritchie et al. 1983a, b; Bigland-Ritchie and Woods 1984). Despite this relationship, it is not the slowing *per se* that causes lowered rates (Bigland-Ritchie et al. 1992a, b), but rather the fatigue-indued changes in the muscle are likely involved (Bigland-Ritchie et al. 1986), which also slow contractile speed (see 'Do motor unit firing rates consistently match contractile speed'). Therefore, despite what appears functionally sensible these concurrent changes could be coincidental. Future studies should separate these phenomena to provide further insight into these apparent interdependencies of fatigue.

Throughout this review, the reduction in MU firing rates during high-intensity contractions has been implicated as a strategic adaptation to mitigate force loss. A contrary interpretation is that the reduced firing rates are a result of impaired descending drive and motoneuron excitability, and therefore, this is not a purposeful and beneficial adaptation, but rather a central limitation (e.g., Taylor and Gandevia 2008). However, it is our view that the data which indicate a limitation of central mechanisms to maintain high firing rates does not challenge the muscle wisdom hypothesis. Notably, the core of the hypothesis states the lowered firing rates observed during high-intensity contractions are preventative and not causative of force loss. Thus, the direct mechanisms in which firing rates are lowered are not focal to the core argument and whether firing rates are moderated through central or peripheral mechanisms is not a principal component of the current hypothesis. Rather, if a central limitation contributes to the reduction in firing rates it could be interpreted that this inability to maintain high rates is a compensatory mechanism to limit peripheral muscle fatigue because if rates do not decline force loss is augmented (Fig. 9). Thus, in this alternative view, if there was no central limitation the maintenance of high firing rates would be detrimental for force preservation.

Maximal isometric contractions as a model for muscle fatigue

By simply defining fatigue as force loss the use of sustained isometric MVCs provides a useful and well-controlled model. With this contraction mode, additional variables such as changes in muscle length or velocity would not influence force (Bigland-Ritchie 1981). As noted by many MVCs have several advantages for studying fatigue (Bigland-Ritchie 1981; Taylor and Gandevia 2008). With an MVC all MUs are presumably activated (at least initially, cf. Amann et al. 2022; Kavanagh et al. 2019) and thus recruitment is better controlled during an acute task (e.g., 1 min), compared to sustained submaximal tasks (Taylor and Gandevia 2008). Furthermore, with submaximal contractions increased neural drive can occur to compensate for contractile impairments, however, during an MVC the task is 'maximal' throughout, and this tests the entire motor pathway (Taylor and Gandevia 2008). Sustained activity was historically preferred as there would be potentially uncontrolled degrees of recovery if intermittent contractions were used. Furthermore, fatigued-related changes in the rate of force development may introduce further issues for controlling contraction duty cycles. Many of the complications are minimized or avoided using isometric MVCs (Bigland-Ritchie 1981). However, the application of these results outside of this contractile paradigm is undetermined. It is well appreciated that fatiguing submaximal tasks impose different MU control strategies (as noted above) and the muscle wisdom hypothesis is unreasonable for this task (Garland and Gossen 2002; Pascoe et al. 2014). This is not surprising because of the task dependency of fatigue and indeed the muscle wisdom hypothesis was formulated in relation MVCs. Although the original muscle wisdom experiments were conducted with sustained contractions (Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983), force is also better preserved with declining rates of stimulation compared to sustained high-frequency rates during intermittent fatiguing contractions of the human quadriceps (Binder-Macleod and Guerin 1990). Although potential limitations (noted above) may be imposed during intermittent contractions this activation pattern better mimics cyclical natural movements. Furthermore, mechanisms that contribute to force loss (see 'Mechanisms for force loss during sustained maximal activation') can have differing importance as blood perfusion is reestablished during rest periods. Regardless, of these differences in activation patterns (i.e., sustained vs intermittent) during high-intensity contraction force is better preserved with declining rates of stimulation. Overall studies across various activation patterns (i.e., sustained vs intermittent), as well as muscle groups (adductor pollicis, dorsiflexors and quadriceps, Bigland-Ritchie et al. 1979; Jones et al. 1979; Marsden et al. 1983; Binder-Macleod and Guerin 1990; Dudani et al. 2025) have supported the significance of the muscle wisdom hypothesis as a basic tenet in helping to explain the neuromuscular factors involved in muscle fatigue during high-intensity activation. More recently, reductions in firing rates with maximal contractions have been replicated with fatiguing dynamic (i.e., joint rotation) contractions at slow and fast velocities (Cowling et al. 2016; Zero et al. 2023b). Indeed, the absolute reduction in rates may be larger than isometric contractions (Cowling et al. 2016) but this requires further investigation. Whether these reductions are coincidental, or purposeful to optimize contractile matching and delay peripheral excitation failure in this or other dynamic tasks remain unclear.

Summary and concluding remarks

It is widely appreciated that several mechanisms contribute to muscle fatigue and the relative importance varies on the task. Through a detailed exploration of historical and current studies regarding the muscular wisdom hypothesis, we indicate that declining MU firing rates during sustained isometric MVCs are preventive and thus not causative of force loss. Electrical propagation of muscle is maintained within the safety factor and provides adequate activation during acute (e.g., 1 min) MVCs and thus does not contribute to force loss. As originally proposed, the declining rates of activation contribute to the preservation of electrical propagation, however, several other mechanisms are also involved. Furthermore, the concurrent slowing of contractile speed and reduction in firing rates contribute to force preservation during this task as originally suggested, although the importance of matching contractile speed to firing rates was initially overstated. Specifically, several other nonlinear history-dependent properties of muscle can maintain force despite a reduction in activation rate and are more potent than slowing alone. Furthermore, it seems unlikely tailored control occurs to provide an optimal input–output relationship of the respective motoneuron and muscle unit which is highly variable among MUs. Although the reduction in firing rate during sustained MVCs does not contribute to force loss, cessation or de-recruitment of MUs may occur which does impair force generation and contributes to reports of impaired voluntary activation.

The experiments forming the muscular wisdom hypothesis have been foundational studies to the field of muscle fatigue and the initial hypotheses proposed recognized the importance of studying a human neuromuscular system. Indeed, with this integrated approach it is not surprising to conclude that "perhaps the neuromuscular system as a whole is so well adjusted that any task-related additional impairment at one site is compensated by corresponding functional improvements at others" (Bigland-Ritchie et al. 1995). The muscle wisdom hypothesis is a classic example of the capable adjustments in response to stress by mitigating impairments at one site through adaptations at another and has spawned many studies to further explore fatigue-related factors in response to contractile failure.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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