An Expansion of Simons' Integrated Hypothesis of Trigger Point Formation

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Simons' integrated hypothesis proposed a model of trigger point (TrP) activation to explain known TrP phenomena, particularly endplate noise. We propose an expansion of this hypothesis to account for new experimental data and established muscle pathophysiology.

Introduction

Myofascial pain syndrome (MPS) is a myalgic condition characterized by local and referred pain that originates in a myofascial trigger point (TrP) [1••]. The term myofascial TrP was coined to describe a zone of intense pain in a hardened muscle band that refers (triggers) pain distantly when stimulated. The active TrP has two clinical attributes that must be explained for there to be a more complete understanding of the nature of myofascial pain. One attribute is a motor dysfunction of the muscle that is characterized by a constant, discrete hardness within the muscle. It usually is palpable as a taut band or nodularity within the belly of the muscle. The other attribute is a sensory abnormality that is characterized primarily by pain. Pain can be local to the site of the taut band and distant from it or referred to another part of the body. The taut band is a constant feature of an active TrP and can be present in the absence of pain. It appears to be the primary abnormality that develops in response to stressors that activate TrP formation. Ischemia may be an important factor in the development of the taut band, if not a dominant factor. The taut band and pain are dynamic features of the muscle TrP. They vary in their presence and activity from being spontaneously painful to being quiescent and painful only when stimulated mechanically or metabolically. The taut band itself has unique characteristics not found in normal muscle. It is persistently hard, is considered to be a contracted band of muscle, and has the additional property of contracting sharply when mechanically stimulated by plucking it manually or by putting a needle into it. The mechanism that underlies development of the taut band is unknown, but altered activity of the motor endplate, or neuromuscular junction, is most likely. Increased concentration of acetylcholine (ACh) in the synaptic cleft, changes in ACh receptor (AChR) activity in a number of receptors, and changes in acetylcholinesterase (AChE) activity are consistent with known mechanisms of endplate function and could explain the increase in endplate electrical activity that is seen in the active myofascial TrP.

Local myofascial pain occurs because of the release of substances from damaged muscle, such as adenosine triphosphate (ATP) [2], bradykinin (BK), 5-hydroxytryptamin (5-HT, serotonin), prostaglandins, and potassium (K^+), and from the extracellular fluid around the TrP, such as protons (H^+), from the acidic milieu, which occurs in ischemia and in exercise. These substances activate muscle nociceptors. They also induce the release of calcitonin gene-related peptide (CGRP) from the motor nerve terminal and from the muscle nociceptors, which in turn increases motor endplate activity.

This article presents known data about the TrP and discusses in detail salient features of muscle contraction, motor endplate function, and some of the biochemical features of receptor function as they relate to the TrP. This information is synthesized into an expansion of the integrated hypothesis of the TrP that has been put forth by Simons *et al.* [1••]. A primary focus of this discussion is the formation and maintenance of the taut band, an early and essential development in the formation of active TrPs.

Features of Myofascial Trigger Points and Muscle Nociceptors

Certain features of the myofascial TrP relevant to the problem of how the taut band develops and is maintained are well established. Likewise, certain pathophysiologic changes in exercised muscle are known that are relevant to the development of muscle pain and MPS. The neurophysiology of sympathetic nerve function and of nociceptive sensory receptor activation and modulation are relevant to an understanding of the TrP. These points are summarized in the next section.

A taut muscle band may contain a latent TrP, without tenderness. However, in MPS, tenderness is always associated with the taut band. Treatment of the tender taut band by injection of local anesthetic, dry needling without anesthetic, or manual compression and stretching of the tender

area in the taut band without use of any anesthetic results in softening of the taut band and an increase in the pressure pain threshold not seen in control, non-tender muscles (Gerwin, unpublished data).

A marked increase in the frequency of low-voltage (50–100 microvolts) electrical activity is found at the point of maximum tenderness in the taut band in the human [3•]. It has been convincingly localized to the neuromuscular junction endplate zone of the taut band, where it appears as an abnormally increased frequency of miniature endplate potentials, in the rabbit model [4,5] and in humans [6•].

Areas of intense focal sarcomere contraction have been described in the muscles of animals with naturally occurring TrPs [7] and in animals in which AChE activity has been pharmacologically blocked or inhibited [8–10]. In the three studies in which AChE was blocked or inhibited, the supercontraction of sarcomeres occurred at the neuromuscular junction. Sarcomere contraction also was noted in two human studies, one a biopsy study and the other on fresh cadavers [11,12].

There are a number of biochemical alterations identified by microdialysis sampling techniques at the active TrP site [13•]. Among the changes found are elevated CGRP levels and acidic pH when compared with inactive (asymptomatic) TrPs and normal control subjects.

Exercise under ischemic conditions [14] and eccentric muscle exercise result in muscle pain. Delayed-onset muscle soreness occurs after ischemic exercise [15] and after eccentric exercise. Muscle that is maximally eccentrically contracted shows evidence of muscle fiber destruction similar to changes seen in exercised ischemic muscle [16,17•,18]. Unaccustomed eccentric exercise (forced lengthening of a contracting muscle) causes immediate damage to the muscle and delayed muscle soreness in the ensuing days. Muscle soreness is the result of local muscle damage, inflammatory changes, and nociceptor sensitization [19,20••]. Metabolic disorders that impair energy production in muscle are associated with exercise-induced muscle pain. Maximal concentric exercise also compresses capillaries and can produce muscle ischemia and injury. Sustained contraction of muscle, commonly seen in postural work-related MPS, is thought to have a similar effect on muscle and blood flow.

Tendon organs (sensory receptors located at the muscle-tendon junction in skeletal muscle) are responsive to active tension generated by contractions of groups of motor units [21]. They are particularly sensitive to active muscle force, but also respond to muscle stretch.

Intramuscular hypoperfusion is likely to occur in myalgic syndromes such as myofascial pain [22,23,24••].

Hypoxia (extremely low PO_2) is associated with the TrP [25]. This is compatible with the concept of circulatory hypoperfusion of TrP-containing muscles because ischemia produces hypoxia.

Individuals with work-related trapezius myalgia have a deficit of cytochrome C oxidase [26,27], which is suggestive of an energy crisis within the muscle, perhaps associated with mitochondrial dysfunction. This correlates with reports of low levels of ATP and adenosine diphosphate in patients with trapezius myalgia. A high degree of mitochondrial disorganization also was seen in the muscles of these patients. Moreover, there was a decrease in the number of capillaries per fiber area in these subjects. These data support the concept of an ischemia-induced energy crisis in the development of exercise-induced muscle pain.

α-Adrenergic agonists that inhibit sympathetic nerve activation reduce abnormal miniature endplate activity by approximately 60% [28•].

Muscle nociceptors are dynamic structures whose receptors can undergo conformational change depending on local tissue environment. Furthermore, individual muscle nociceptors possess vanilloid (sensitive to heat, H^+), purinergic receptors (sensitive to ATP, adenosine diphosphate, and adenosine) and acid-sensing ion channels (ASIC) [20••]. Therefore, the same nociceptor is capable of transmitting pain during inflammation through the vanilloid receptor and ASIC and pain caused by muscle trauma or other cases of muscle necrosis through the purinergic receptor.

The nociceptor terminal contains stored substances, (*eg*, substance P [SP] and CGRP). Although these substances are produced in the dorsal root ganglion, 90% of the SP and CGRP is transported antidromically down the axon into the nociceptor terminal from where they are tonically released. However, a noxious stimulus sufficient to cause nociceptor activation causes bursts of SP and CGRP to be released into the muscle. They have a profound effect on the local biochemical milieu and microcirculation by stimulating "feed-forward" neurogenic inflammation (a continuous cycle of increasing production of inflammatory mediators and neuropeptides and increasing barrage of nociceptive input into wide dynamic-range neurons in the spinal cord dorsal horn).

Implications

Taken together, these points suggest that a possible activating event in MPS is exercise under conditions that limit the availability of an energy supply, possibly by the development of high pressures within the contracting muscles that result in vascular constriction or closure and the subsequent development of muscular ischemia and cell damage. Damaged muscle releases inflammatory mediators that activate muscle nociceptors to increase the release of neuropeptides locally and in the dorsal horn. A critical review of the relation of hypoperfusion to chronic muscle pain recently has been published [24••], accompanied by two very cogent commentaries [29,30] in which the pros and cons of such a theory are argued. There certainly is confounding and conflicting data on this topic. Nevertheless, there are some attractive features of this hypothesis as it relates to the development of the taut band.

The increase in CGRP that occurs in ischemia-induced muscle injury could result in an apparent increase in AChR

activity and an inhibition of AChE activity, resulting in the development of the taut bands seen in MPS. The mechanism whereby the sympathetic nervous system modulates endplate noise has been unexplained previously. Adrenergic activity can alter the release of ACh from the motor nerve terminal. It also can produce vasoconstriction through desensitization and down-regulation of β_2-adrenoreceptors or an up-regulation of α_2-adrenoreceptors [24••]. Superimposed on other factors that predispose to focal hypoperfusion, it can turn a marginal state of ischemia into a pathologic state.

The work of Shah *et al.* [13•] sheds light on the nature of the active TrP and on the development of the taut band and muscle tenderness. Preliminary results of studies on the local biochemical milieu of the TrP using microdialysis sampling techniques show that at the active TrP, the pH is lowered and that SP, CGRP, BK, norepinephrine, 5-HT, tumor necrosis factor-1α, and interleukin 1 are significantly higher compared with latent TrPs and with normal control subjects [13•]. The role that some of these factors play in the activation of the taut band and in the initiation and perpetuation of muscle pain is discussed in this paper.

Muscle Injury Related to Eccentric Muscle Contraction and Maximal Concentric Muscle Contraction

Unaccustomed or intense exercise-induced weakness and muscle damage is well documented, particularly for eccentric exercise [31]. Eccentric muscle contraction is muscle contraction of a lengthening muscle. Examples that illustrate lengthening contractions are laying a heavy object on a table while extending the contracting biceps muscle as the arm extends at the elbow. Another is that of a water skier rising out of the water while skiing, lengthening the contracting hamstrings as the knees and hips both extend. A final example is walking or running downhill, an action that is accomplished with lengthening contractions of the quadriceps.

Eccentric exercise is associated with muscle soreness and muscle damage. Immediate injurious effects occur with as little as one unaccustomed eccentric contraction in unconditioned muscle, resulting in delayed onset muscle soreness. This produces pain with stretching or muscle contraction or with muscle palpation. Eccentric exercise causes an irregular and uneven lengthening of muscle fiber and overextension of some sarcomeres to a point beyond filament overlap. Lengthening of muscle to this point is beyond the optimum length/tension ratio, which is a region of sarcomere length instability. Recovery of muscle contractibility is impaired in the range beyond the optimum length/tension ratio. Therefore, optimum length for active tension of a contracting muscle unit is an important factor in determining whether there will be tissue damage. A muscle unit that has an optimum length less than the whole muscle optimum length is more likely to be damaged [32] because it will reach a point of instability before the whole muscle does. Different muscle fiber length-tension relationships throughout the muscle are considered to be a reason that muscle fiber injury with eccentric exercise is uneven [21] and nonhomogeneous within the muscle. This may be clinically important because the taut band in muscle is not uniformly distributed throughout the muscle, perhaps reflecting the heterogeneous distribution of muscle injury.

Muscle fiber injury occurs rapidly in eccentric muscle contraction. Desmin is a muscle cytoskeletal protein that transmits force from myofibrillar force generators (actin and myosin) to the muscle surface and to the muscle-tendon junction. It is lost soon after eccentric muscle contraction and is one of the earliest signs of muscle damage. Loss of the desmin protein results in significant disorganization of the myofibrillar lattice [33]. A significant loss of desmin staining was seen 5 minutes after initiation of eccentric exercise [34]. Loss of desmin staining occurred in the absence of contractile or metabolic protein disruption, thereby indicating that it is one of the first signs of injury in eccentric contraction. A single bout of eccentric exercise in rats resulted in early loss of desmin, inflammatory cell infiltration, and transient increase in membrane permeability, but ultimately to an increase in desmin content per sarcomere [35]. Segmental disruption of muscle occurs with a loss of cellular integrity and an increase in fiber size caused by the segmental hypercontraction of muscle fiber that is associated with very short sarcomere lengths [36]. These authors concluded that after eccentric muscle contraction, the muscle fiber cytoskeleton is disrupted, Z-band streaming occurs, and the A-band is disorganized. Muscle cell integrity is lost, there are hypercontracted regions of muscle, and inflammatory cellular invasion of the muscle fiber occurs. That desmin protein is lost in eccentric contractions has been disputed. A study of human subjects performing eccentric exercises did not show loss of desmin [37]. It is proposed that the absence of staining for titin, actin, and nebulin not associated with Z-band streaming, but seen in regions of increased numbers of sarcomeres, represents adaptation of unaccustomed exercise by new sarcomere formation in humans [38,39]. It is unknown if there is a species difference in response to eccentric exercise or if there is another explanation for these results. Nonetheless, pressure pain thresholds decreased in human subjects performing slow eccentric exercise and a ropy band was felt at the site of pain [40], indicating that eccentric exercise in humans results in nociceptor sensitization and taut band formation.

The regions of sarcomere disruption are thought to act as foci for further damage with repeated, unaccustomed eccentric exercise [21]. Repeated eccentric contractions lead to sarcomere breakdown and muscle fiber damage [17•,19,41]. Maximal concentric and eccentric exercise damage sarcoplasmic and endoplasmic reticulum in skeletal muscle. Muscle protein oxidation is produced in every form of exhaustive exercise, including eccentric exercise

[42]. Increased muscle fiber tension or contraction tension develops after injury to even a few muscle fibers. The increase in passive tension of the muscle is associated with an increase in sarcoplasmic Ca^{++}, causing a sensation of muscle stiffness. Causes of muscle injury with eccentric exercise are thought to include free radical cellular injury from the increased production of reactive oxygen species that induces neutrophil and macrophage migration, infiltration, and cytokine activation [43,44]. Increase in free radical production is associated with lipid peroxidation that further contributes to muscle fiber injury [45].

One result of muscle damage is an immediate reduction of muscle force-generating capacity [31]. The clinical manifestation of this is weakness. The TrP is associated with weakness, but there must be a reversible motor inhibitory component to the weakness, perhaps central at the spinal cord level, because there is an almost instantaneous restoration of strength when the TrP is inactivated. This clinical observation contrasts with the structural changes associated with myofibril cellular damage, changes that would not reverse quickly.

Calcitonin Gene-related Peptide, Acetylcholine Receptors, and Acetylcholinesterase

Calcitonin gene-related peptide

Calcitonin gene-related peptide coexists with ACh at the synaptic endings of the motor nerve and acts as a facilitator of ACh release from the motor nerve fiber terminal. It is released by electrical stimulation of the nerve ending or by the accumulation of ACh that may be induced by inhibition of AChE. CGRP is a 37 amino-acid peptide that has multiple known activities. It is a vasodilator, augments autonomic functions, affects immunologic function, and modulates neurotransmission at central and peripheral synapses. It is present in two forms: CGRP 1 and 2. The two forms differ by only a few amino acids and are encoded by different genes that are separately regulated. The metabolism of AChR molecules and of AChE molecular forms are partly controlled by the activation of CGRP-1 binding sites. High-affinity CGRP-1 binding sites in the adult rat gracilis muscle are restricted to the motor endplate regions [46••].

Calcitonin gene-related peptide receptors consist of protein complexes that span the membrane and are associated with accessory proteins that include a receptor activity-modifying protein and a receptor component protein that couples the receptor to the cellular signal transduction pathway. The pharmacology of CGRP receptor subtypes is strongly dependent on these accessory proteins. CGRP 1 is made in the anterior horn motor neuron cell body and then moved by axoplasmic flow to the nerve terminal. CGRP-1 activity is up-regulated by axotomy or neuronal blockade. CGRP 1 also enhances AChR-α subunit mRNA in skeletal muscle, increases AChR phosphorylation (the rate of AChR desensitization), and prolongs the mean open time of AChR channels [45]. These functions indicate that CGRP 1 functions to control the synthesis of AChR and activity at the motor endplate. CGRP also controls AChE activity at the neuromuscular junction [47]. CGRP 1 down-regulates all of the AChE molecular forms at the motor endplate. This activity is mediated by specific CGRP-1 receptors [47].

Calcitonin gene-related peptide increases the contractile force of nerve-induced muscle contraction gland, increases cyclic adenosine monophosphate, which regulates AChR phosphorylation and desensitization in a rat model and leads to the accumulation of AChRs on chick embryo myotubes [48]. CGRP up-regulates AChR concentration on the postsynaptic membrane and potentiates the AChR-operated slow Ca^{++} signal by activation of the protein kinase-A system [49]. CGRP has an innervation-like effect on AChE at the motor endplate. CGRP down-regulates AChE, while ACh has the effect of up-regulating AChE activity. AChE production is increased by denervation and by exercise and is decreased by CGRP [48]. The increase in intracellular cyclic adenosine monophosphate also has the effect of down-regulating AChE expression at the transcriptional level, thereby locally inhibiting AChE activity [50]. Thus, CGRP increases the motor endplate receptor sites that serve as docking sites for ACh, increasing the activity of the ACh molecules that are in the synaptic cleft fluid at the postsynaptic membrane.

Calcitonin gene-related peptide increases or decreases ACh release from motor nerve terminals as a species-specific action. Moreover, its action on the same tissue has been reported to be directly opposite. In one study of rat diaphragm, CGRP enhanced ACh release accompanied by an increase in the frequency of miniature endplate potentials [51]. On the other hand, another study reported that CGRP reduced the release of ACh from rat diaphragm [52], although the reverse has been found in mouse diaphragm. The effect of CGRP in some species may be to first depress nerve-evoked ACh release to prevent excessive action of ACh at the neuromuscular synapse; however, subsequently it may enhance muscle contraction [52]. In general, CGRP enhances spontaneous release of ACh from the motor nerve terminal and it binds to high affinity receptors other than the AChR on the postsynaptic membrane near the motor endplate. It also increases the levels of surface AChR on the muscle.

Acetylcholine receptors

The AChR is a transmembrane complex that has an outer ligand-binding configuration, an intramembrane component with different voltage-gated ion channels, and an inner cytoplasmic tail. Therefore, along with motor endplate activity, it is dynamic rather than static. Activation of the motor endplate gives rise to miniature endplate activity or depolarization of the muscle fiber membrane. Miniature endplate activity depends on the state of the AChR and on the local concentration of ACh that is the result of ACh

release, reuptake, and breakdown by AChE. Likewise, depolarization of the postsynaptic membrane and muscle contraction is a result of the interplay between ACh release, the number of available binding sites (AChR concentration), and AChE activity, as well as a number of factors that affect binding and dissociation, such as the affinity of ACh for the receptor and gating kinetics at the AChR [53]. AChR activity is affected by changes in conformation and in the up- and down-regulation of receptor concentration at the motor endplate. Factors affecting receptor activity include physical factors such as temperature and changes in local pH, which can be caused by ischemia, responses to endogenous substances such as peptides released into the local environment, and changes induced pharmacologically.

When the AChR is activated, ionic channel currents are generated that result in miniature endplate potentials or muscle fiber depolarization. Miniature endplate currents depend on the rate constants of ACh binding to AChR. Binding constants related to the affinity of ACh for the receptor are different when AChE is active and when it is inhibited.

Acetylcholine release

Acetylcholine release is quantal and nonquantal. Quantal release is calcium-dependent whereas nonquantal release is calcium-independent. ACh release is partly spontaneous and triggered by motor nerve activation. It also is increased as a result of AChE inhibition that causes accumulation of ACh in the synaptic cleft and stimulates motor nerve endings [54]. Therefore, altered AChE activity is a potential source of endplate activity modulation.

Muscle contraction takes place through depolarization of the muscle fiber membrane at the motor endplate. Quantal ACh, which is ACh in a presynaptic terminal vesicle, is released from the synaptic terminal of the motor nerve and then is taken up by ACh nicotinic receptors in the postsynaptic membrane of the muscle. The quantal release of ACh from synaptic vesicles can result in miniature endplate potentials that are associated with changes in ionic channel currents. Nonquantal release of ACh is leakage of individual molecules of ACh from the motor nerve presynaptic terminal and is not nerve-excitation induced. Spontaneous release of ACh is more nonquantal than quantal. The critical factor in the exocytotic synchronized quantal release of ACh from the motor nerve terminal is the influx of calcium across the membrane [55], mediated by P-type calcium channels.

Acetylcholine also acts through a feedback mechanism to regulate its own release at the neuromuscular junction in the rat [56]. ATP is co-released with ACh during quantal exocytosis and undergoes hydrolysis to adenosine [55]. Evoked quantal ACh release is modulated further by adenosine and by ATP, leading to inhibition and facilitation of ACh release in different species. Nonquantal release of ACh can trigger subthreshold miniature endplate potentials without depolarizing the membrane that results in muscle cell contraction. Many different mechanisms exist that modulate the quantal release of ACh from the presynaptic nerve terminal and influence the frequency of ACh-induced miniature endplate noise.

Presynaptic sympathetic nerve modulation of acetylcholine release

The sympathetic nervous system modulated the observed endplate noise at the TrP, reducing it by approximately 60% in the study by Chen *et al.* [28•]. Alpha-and β-adrenoreceptors on the motor nerve terminal mediate facilitation at motor endplates, enhancing stimulated ACh release from the rodent phrenic nerve [56]. This action provides one mechanism for the observed increase in endplate noise with sympathetic activation and the reduction in endplate noise when sympathetic activity is blocked.

Acetylcholinesterase

Acetylcholinesterase is present in the synaptic cleft. It breaks down ACh and thereby can inhibit or terminate ACh action at the postsynaptic neuromuscular junction. It acts to decrease the available ACh and to inhibit miniature endplate potential activity and motor endplate-induced muscle cell membrane depolarization. AChE activity is pH-dependent. It is inhibited by acidic pH. Therefore, it is inhibited by muscle ischemia and by exercise that is sufficient to lower pH into the acidic range. Furthermore, CGRP down-regulates and thereby effectively inhibits the activity of AChE. CGRP release is augmented by low pH. Thus, the acidic pH found at the active TrP site by Shah *et al.* [13•] favors increased ACh activity through decreasing the action of AChE, but also decreases the removal of ACh from its postsynaptic receptor.

Acidic pH and Muscle Pain

The work of Sluka *et al.* [57••] elegantly demonstrates that acidic pH has a profound effect on the initiation and perpetuation of muscle pain. Repeated acid injections into rat muscle produces a bilateral, long-lasting, mechanical hyperalgesia that is maintained without continued muscle nociceptive input and does not produce damage to muscle tissue. This model also demonstrated that secondary mechanical hyperalgesia is maintained by neuroplastic changes in the central nervous system, even after the cessation of nociceptive activity. The initiation of hyperalgesia occurs in response to repeated intramuscular injection of pH-4 saline, suggesting that initiation involves activation of ASICs or the capsaicin-sensitive TRPV1 channel in muscle. As stated by Sluka *et al.* [58], a more acidic milieu may activate ASIC1 or ASIC3 muscle nociceptors, which in turn could produce mechanical hyperalgesia. Mechanical hyperalgesia is characteristic of the myofascial TrP (Fig. 1).

Hypothesis

It can be hypothesized that the activating event in the development of the TrP is the performance of unaccustomed

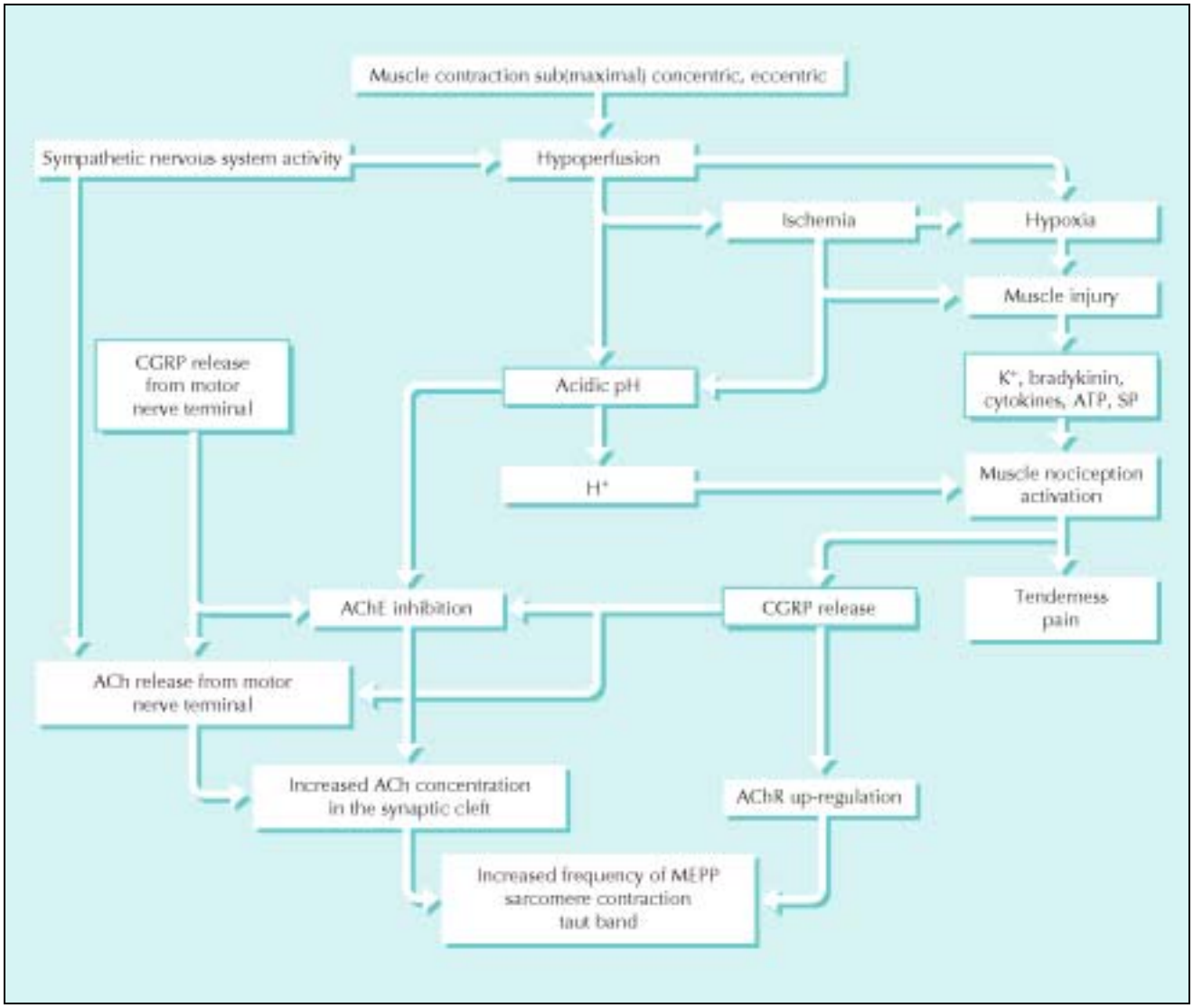

Figure 1. A schematic outline of the expanded trigger point hypothesis. The activating event is muscle activity that stresses muscle beyond its tolerance and leads to muscle injury and capillary constriction. Muscle injury results in the release of substances that activate muscle nociceptors and cause pain. Capillary constriction occurs as a result of muscle contraction and sympathetic nervous system activation. Ischemia results from hypoperfusion, which is caused by capillary constriction. The pH becomes acidic, inhibiting AChE activity. CGRP is released from the motor terminal and from injured muscle. CGRP inhibits AChE, facilitates ACh release, and up-regulates AChRs. The end result is increased ACh activity with increased frequency of MEPPs, sarcomere hypercontraction, and the formation of taut bands. The highlighted boxes indicate those events that have been identified or are supported by microdialysis studies of the trigger point. Ach—acetylcholine, AChE—acetylcholinesterase, AChR—acetylcholine receptors, ATP—adenosine triphosphate, CGRP—calcitonin gene-related peptide, H^+—protons, K^+—potassium, MEPP—miniature endplate potentials, SP—substance P. *Adapted from* Shah *et al.* [13•].

eccentric exercise, eccentric exercise in unconditioned muscle, or maximal or submaximal concentric exercise that leads to muscle fiber damage and to segmental hypercontraction within the muscle fiber. Adding to the physical stress of such exercise is hypoperfusion of the muscle caused by capillary constriction, which results from muscle contraction. Capillary constriction is increased by sympathetic nervous system adrenergic activity. The resultant ischemia and hypoxia adds to the development of tissue injury and produces a local acidic pH with an excess of protons. Acidic pH results in inhibition of acetylcholinesterase activity, increased release of CGRP, and activation of ASIC on muscle nociceptors. Acidic pH alone (in the absence of muscle damage) is sufficient to cause widespread changes in the pain matrix. However, the breakdown of muscle fibers results in the release of several proinflammatory mediators such as SP, CGRP, K^+, 5-HT, cytokines, and BK that profoundly alter the activity of the motor endplate and activity/sensitivity of muscle nociceptors and wide dynamic-range neurons. Motor endplate activity is increased because of an apparent increase in the activity of ACh. This apparent increase in effectiveness is caused by several factors that include an increase in the release of ACh that is mediated by CGRP, presynaptic motor terminal adrenergic receptor activity, and by AChE inhibition caused by CGRP

and acidic pH. AChRs are up-regulated through the action of CGRP, creating more docking sites for ACh, thereby increasing the efficiency of binding to the receptor. The taut band results from the increase in ACh activity. Miniature endplate potential frequency is increased as a result of greater ACh effect. Release of BK, K^+, H^+, and cytokines from injured muscle activates the muscle nociceptor receptors, thereby causing tenderness and pain. The presence of CGRP drives the system to become chronic, potentiating the motor endplate response and potentiating, with SP, activation of muscle nociceptors. The combination of acidic pH and proinflammatory mediators at the active TrP contributes to segmental spread of nociceptive input into the dorsal horn of the spinal cord and leads to the activation of multiple receptive fields. Neuroplastic changes in dorsal horn neurons occur in response to continuous nociceptive barrage, causing further activation of neighboring and regional dorsal horn neurons that now have lower thresholds. This results in the observed phenomena of hypersensitivity, allodynia, and referred pain that is characteristic of the active myofascial TrP.

Conclusions

There normally is an equilibrium between the release of ACh, the breakdown of ACh, and its removal from AChRs in the postsynaptic membrane by AChE that is disturbed with muscle injury. In injured muscle, there is release of substances that activate muscle nociceptors and cause pain and there is facilitation of ACh release, inhibition of ACh breakdown and removal from the AChR, and an up-regulation of AChRs. This leads to the development of persistent muscle fiber contraction, as is characteristic of the myofascial TrP. This hypothesis supports and expands on the main theses of Simons' pioneering Integrated Trigger Point Hypothesis and points to further areas of needed investigation.

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