

Travell Trigger Points—Molecular and Osteopathic Perspectives

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The proposed etiology of Travell trigger points (TrPs) has undergone a fundamental revision in recent years. New research results suggest that TrPs are evoked by the abnormal depolarization of motor end plates. This article expands the proposed etiology to include presynaptic, synaptic, and postsynaptic mechanisms of abnormal depolarization (ie, excessive release of acetylcholine [ACh], defects of acetylcholinesterase, and upregulation of nicotinic ACh-receptor activity, respectively).

This working hypothesis regarding the etiology of TrPs has changed the approach to treating TrPs. As an example, Travell and Simons abandoned the application of ischemic compression to TrPs; instead the authors adopted several techniques associated with osteopathic medicine (ie, muscle-energy, myofascial, counterstrain; high-velocity, low-amplitude). Scientists are now proposing and reporting the results of new approaches using capsaicin, a vanilloid-receptor agonist, and ACh antagonists (eg, dimethisoquin hydrochloride, botulinum toxin, quinine, linalool). The purpose of this article is to review these new concepts and describe new resulting approaches to the treatment of TrPs.

Janet G. Travell, MD, (1901–1997) was an internist in general medicine who developed an interest in spinal manipulation in the 1940s,¹ but later shifted her focus to myofascial trigger points (TrPs). In 1955, she relieved then-Senator John F. Kennedy of disabling back pain (after he endured a failed diskectomy in 1944 and laminectomy in 1954).² Travell's ensuing post as White House physician, followed by the publication of her two-volume "Red Bible," *Myofascial Pain and Dysfunction: The Trigger Point Manual*,^{3,4} coauthored with David G. Simons, MD, brought prominence to her approach for treating TrPs.

Travell defined a TrP as "a hyperirritable spot in skeletal muscle that is associated with a hypersensitive palpable nodule in a taut band. The spot is tender when pressed and can give rise to characteristic referred pain, motor dysfunc-

tion, and autonomic phenomena."⁵ An example of this is shown in *Figure 1*. The taut band of muscle is best characterized as a palpable, ropy structure.

Palpation is a reliable diagnostic criterion for locating TrPs in patients.⁶ The reliability of diagnosing TrPs is similar to the reliability of diagnosing tender points in the counterstrain system developed by Lawrence H. Jones, DO.⁷ An interrater-reliability study of this counterstrain system demonstrated that clinicians agreed 73% of the time ($\kappa = 0.45$); the palpation of patients' TrPs proved more reliable than the standard osteopathic TART examination.⁷ (TART is a mnemonic for the four criteria of somatic dysfunction: tissue texture abnormality, asymmetry, restriction of motion, and tenderness.⁷)

Myofascial trigger points can be inactivated by a variety of approaches, including osteopathic manipulative treatment (OMT), massage therapy, ultrasound therapy, "spray and stretch," as well as needling (acupuncture or injection). A full account that describes the diagnosis and treatment of Travell TrPs is provided by Kuchera and McPartland in *Foundations for Osteopathic Medicine*.⁸ This article serves as a companion piece to Kuchera and McPartland's chapter in *Foundations*, describing a new working hypothesis regarding the etiology of TrPs and the way in which this new hypothesis changes our treatment of these points. Most of the material in this article was mistakenly deleted from the final version of the *Foundations* chapter.

Proposed Etiology of TrPs

The 1999 edition of *Travell and Simons' Myofascial Pain and Dysfunction: The Trigger Point Manual*⁵ proposes an "integrated hypothesis" regarding the etiology of TrPs. Such an integrated hypothesis involves local myofascial tissues, the central nervous system (CNS), and biomechanical factors.

A biopsy of local myofascial tissue in the vicinity of TrPs revealed that the tissues contained "contraction knots," described as "large, rounded, darkly staining muscle fibers and a statistically significant increase in the average diameter of muscle fibers."⁹ Electromyographic (EMG) studies of TrPs have indicated spontaneous electrical activity (SEA) in TrPs, while adjacent muscle tissues are electrically silent.¹⁰ These intersecting discoveries led Travell and Simons to implicate dysfunctional motor end plates as the underlying etiology of TrPs. The terms *motor end plates* and *neuromuscular junction*

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are interchangeable, although the first term describes structure and the latter reflects function. Both terms refer to the point where α -motor neurons contact their target muscle fibers. (See *Figure 2* for a schematic drawing of a motor end plate.) The correlation between motor end plates and TrPs (“myalgic spots”) was first elucidated in a study conducted by Gunn and Milbrandt in 1977.¹¹

Travell and Simons attributed motor end plate dysfunction to an excessive release of acetylcholine (ACh) from the presynaptic motor nerve terminal.^{5,9} Acetylcholine released into the synaptic cleft rapidly activates nicotinic ACh receptors (nAChRs) on the postsynaptic muscle membrane, leading to a muscle action potential and muscle contraction (*Figure 2*). Travell and Simons’ hypothesis of a presynaptic dysfunction, however, is only one way to interpret the results of EMG studies. As the EMG electrodes are placed in postsynaptic muscle fibers, the increased SEA measured in TrPs could be attributed to the result of presynaptic, synaptic, or postsynaptic dysfunction.⁵ All of these dysfunctions can be inherited (genetic) or acquired.

Genetic Defects

Gene mutations frequently arise as nucleotide polymorphisms (SNPs, pronounced “snips”) and microsatellite polymorphisms. Single nucleotide polymorphisms are common deoxyribonucleic acid (DNA) variations among individuals, caused by a single-point mutation. Microsatellite polymorphisms are mutated DNA loci that contain nucleotide repeats. Pellegrino et al¹² implicated genetic factors in the formation of TrPs.

Genetic defects of motor end plates can be presynaptic, synaptic, or postsynaptic.¹³ Presynaptically, the release of ACh depends on the calcium ion (Ca^{2+}) concentration in the α -motor nerve terminal. Excessive release of ACh may be caused by defects of L-type and N-type voltage-gated Ca^{2+} channels.¹⁴ An Internet search of the SNP catalog maintained by the National Center for Biotechnology Information (available at: <http://www.ncbi.nlm.nih.gov>) reveals 695 reports of L-type Ca^{2+} channel mutations and 57 reports of N-type Ca^{2+} channel mutations. Thus, a genetic cause for excess ACh release may be quite common.

Synaptically, ACh is normally inactivated by the enzyme acetylcholinesterase (AChE) (*Figure 2*). Genetic defects of AChE may cause excess ACh to remain in the synaptic cleft.¹³

Postsynaptically, a gain-of-function defect of nAChR may confer muscle hyperexcitability, a hallmark of Travell TrPs. The nAChR is an assembly of 5 subunits; at least 16 genes encode nAChR subunits that combine in a variety of ways.¹⁵ Thus, nAChR is particularly susceptible to mutation defects. The nAChR in the motor end plate expresses different subunits than nAChR expressed in the CNS or in the autonomic nerves. Gain-of-function mutations result in the overexpression of nAChRs in the muscle cell membrane, as well as resulting in nAChRs that are hypersensitive to ACh. These mutations also result in nAChRs that become constitutively active.¹⁶

Acquired Defects

Many ion channels and neuroreceptors are expressed by more than one gene. These genetic subtypes are expressed in cells in different parts of the body for different needs and at different points in the life cycle. Dysregulated expression of these genes will produce acquired defects. To illustrate this mechanism, consider the 16 genes that encode nAChR subunits. The gene that encodes a CNS nAChR may become dysregulated in a muscle cell and may begin producing CNS nAChRs in the motor end plate. Couple this dysfunction with tobacco smoking. Nicotine normally activates CNS AChRs and not motor end plate AChRs. If dysregulated, however, CNS nAChRs become expressed in motor end plates. Nicotine would then activate those receptors in motor end plates, potentially causing TrPs.

Single genes may also become dysregulated should they express splice variants. Splice variants are alternative ways in which a gene’s protein-coding sections (exons) are joined together to create a messenger ribonucleic acid molecule and its translated protein. For example, AChE expresses several subtypes that are produced by alternative splicing of the single AChE gene.¹⁷ These subtypes are induced under psychological, chemical, and physical stress.¹⁸

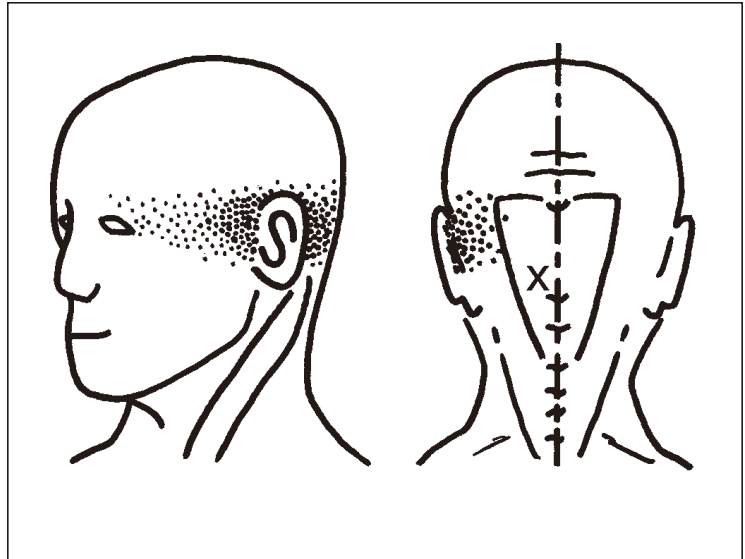
The simple upregulation of certain genes may lead to muscle hyperexcitability and evoke TrPs in muscles. For example, L-type and N-type Ca^{2+} channels are upregulated by factors associated with physical and psychological stress,^{19,20} as well as by nicotine.²¹ Patients with TrPs and long-term musculoskeletal pain should avoid tobacco smoking, as well as excess caffeine.²² Caffeine upregulates activity at motor end plates by acting as an agonist of ryanodine receptors²³ and an antagonist of adenosine A2A receptors.²⁴

Motor End Plate Dysfunction Cascade

When a motor end plate becomes dysfunctional, several perverse mechanisms cause it to persist as a TrP. The excessive muscle contraction compresses local sensory nerves, which reduces the axoplasmic transport of molecules that normally inhibit ACh release.^{25,26} The sustained muscle contraction also compresses local blood vessels, reducing the local supply of oxygen. This impaired circulation, combined with the increased metabolic demands generated by contracted muscles, results in a rapid depletion of local adenosine triphosphate (ATP). The resultant “ATP energy crisis”⁵ triggers presynaptic and postsynaptic decompensations. In the nerve terminal, ATP directly inhibits ACh release,²⁷ so depletion of ATP increases ACh release. In the muscle cell, ATP powers the Ca^{2+} pump, which returns calcium to the sarcoplasmic reticulum. Hence, loss of ATP impairs the reuptake of Ca^{2+} , which increases contractile activity—a vicious cycle.⁹

The ATP energy crisis cascades into a local release of chemicals that activate or sensitize nociceptive nerves in the region, including bradykinins, cytokines, serotonin, histamine, potassium, prostaglandins, leukotrienes, somatostatin, and

Figure 1. Trigger point of the left rectus capitis posterior major (marked by an X) and its referred pain pattern (stippling). (Adapted in part from Travell et al.³)



substance P.⁹ This chemical activation and sensitization of nociceptors accounts for TrP tenderness. Sensitizing substances may also generate a focal demyelination of sensory nerves. Demyelination creates abnormal impulse-generating sites (AIGS) capable of generating ectopic nociceptive impulses.²⁸

CNS and Biomechanical Factors

The CNS and biomechanical factors also contribute to the formation and maintenance of TrPs. A persistent barrage of nociceptive signals from TrPs will eventually sensitize the CNS, a process termed *central sensitization*. This process accelerates in the presence of AIGS and their associated ephaptic crosstalk (cross-excitation) with neighboring autonomic nerves. Travell and Simons’ view of the CNS as an “integrator” of TrPs is interchangeable with Korr’s description²⁹ of the CNS as an “organizer” of somatic dysfunction. According to Travell and Simons, the sensitized dorsal horn becomes a “neurologic lens,” consolidating other nociceptive signals converging on the same segment of the spinal cord, including other somatic dysfunctions and visceral dysfunctions.⁵

Biomechanical factors that stress muscles (eg, acute trauma, repetitive microtrauma) contribute to TrP dysfunction. Further, biomechanical stress of a cold muscle is a key factor in the formation of TrPs,³⁻⁵ as cooling muscles apparently upregulate nAChR activity at the motor end plates.³⁰ The revised edition of Travell and Simons’ manual emphasizes the relationship between TrPs and nearby articular dysfunctions. In the manual, the authors correlate suboccipital TrPs with occipitoatlantal (OA) dysfunctions, semispinalis capitus TrPs with OA dysfunctions and atlantoaxial dysfunctions, and splenius TrPs with upper thoracic articular dysfunctions.⁵

Postural disorders often contribute to the perpetuation of TrPs. For example, postural strain of the suboccipital muscles may cause TrPs in these muscles,⁵ leading to further deterioration in muscle structure and function. Such deterioration

may result in radiating pain (Figure 1) and atrophic changes.³¹ Suboccipital muscles contain a high density of proprioceptors,³² so atrophic changes lead to a loss in proprioceptive balance and loss of proprioceptive “gate control” at the dorsal horn, giving rise to chronic pain syndromes.³¹

Considerations for Osteopathic Medicine

Twenty years ago, Travell and Simons treated TrPs with “ischemic compression” by applying heavy thumb pressure on TrPs, sufficient to produce skin blanching.³ In the 1999 edition, Travell and Simons recommend applying gentle digital pressure to TrPs.⁵ This fundamental change is anchored in Travell’s ATP energy crisis model, which characterizes TrPs as centers of tissue hypoxia. Thus, deep digital pressure that produces additional ischemia is not beneficial. Travell and Simons named their new technique “trigger point pressure release.”⁵ Applying a “press and stretch” technique is believed to restore abnormally contracted sarcomeres in the contraction knot to their normal resting length. It is an indirect technique that uses the barrier-release concept, in which the finger “follows” the releasing tissue.

During the past 20 years, Travell and Simons developed an appreciation for OMT, though they learned of it from European allopathic physicians. The authors began treating TrPs with a muscle-energy technique they called the “Lewit technique.”³ Karl Lewit, MD, from the Czech Republic, developed his technique after working with Fred L. Mitchell, Jr, DO, Philip E. Greenman, DO, and other osteopathic physicians.³³ A Dutch variation of Lewit’s method, the “Gaymans-Lewit technique,” evolved after Gaymans met osteopathic physicians in New York City in the early 1970s.³⁴ Travell and Simons subsequently cited Mitchell and Greenman and described muscle energy and myofascial release.⁴

Travell and Simons’ revised edition of their manual advocates muscle energy, counterstrain, myofascial release, and

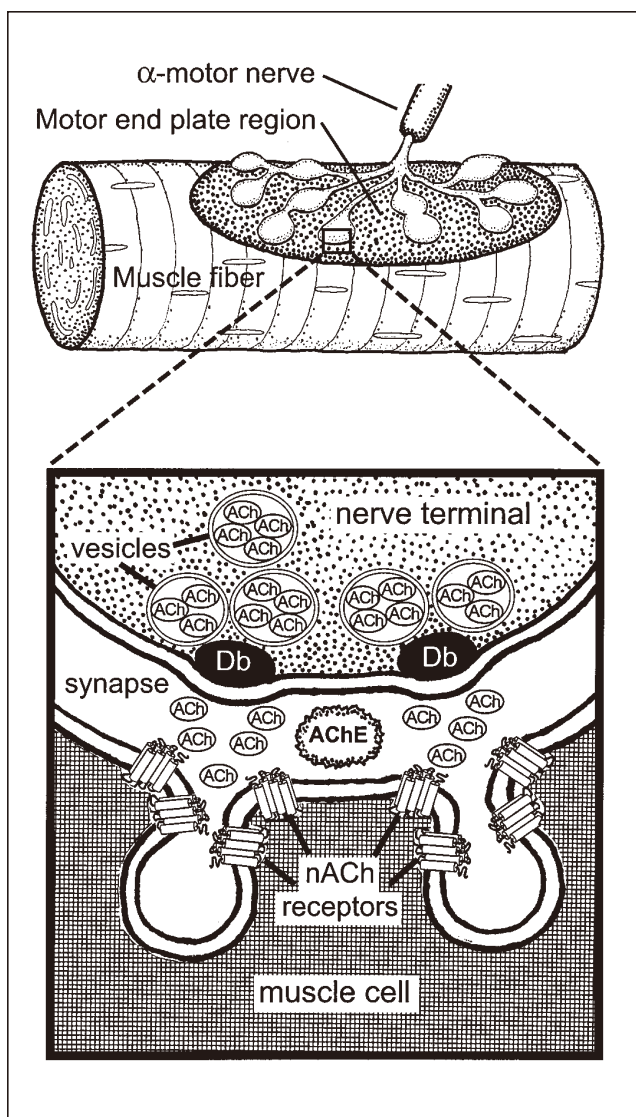


Figure 2. The motor end plate—proposed site of trigger point dysfunction.

Top illustration: The junction between the α -motor neuron and the muscle fiber. The α -motor neuron terminates in multiple swellings termed synaptic boutons. Bottom illustration: presynaptic boutons are separated from the postsynaptic muscle cell by the synaptic cleft. Within each bouton are many synaptic vesicles containing ACh, clustered around dense bars (Db). The Db is the site of ACh release into the synapse. Across the synapse from the Db, the postsynaptic muscle cell membrane forms junctional folds that are lined with nicotinic ACh receptors (nACh). ACh released into the synapse activates nACh receptors, then is inactivated by the acetylcholinesterase enzyme (AChE). (Adapted in part from Kandel et al.⁵⁸)

other OMT techniques for treating TrPs and associated articular somatic dysfunctions.⁵ In addition, high-velocity, low-amplitude thrust techniques are illustrated, harkening back to Travell's early interest in spinal manipulation.¹

Other New Approaches for Treating TrPs

Travell and Simons recommend dimethisoquin hydrochloride ointment (Quotane) for massaging TrPs in superficial muscles such as the orbicularis oculi, frontalis, and occipitalis.³ Dimethisoquin, a local anesthetic, inhibits voltage-gated Na^+ channels (conferring its anesthetic effect) but also acts as a noncompetitive inhibitor of nAChRs ($\text{IC}_{50} = 2.4 \mu\text{M}$).³⁵ The anesthetic's potency is significantly greater than that of lidocaine ($\text{IC}_{50} = 52 \mu\text{M}$) and procaine ($\text{IC}_{50} = 240 \mu\text{M}$). Further, dimethisoquine is uniquely selective for the nAChR subtype expressed in the neuromuscular junction.

Massage with capsaicin cream (0.075%, available over the counter) is useful for treating TrPs located in surgical scars,³⁶ which are particularly refractory to treatment.⁵ Capsaicin selectively binds to the vanilloid receptor (VR1).³⁷ Vanilloid-receptor activation triggers an influx of Ca^{2+} into neuron terminals, which initiates neurotransmitter release. Repeated exposure to capsaicin, however, causes VR1s to become desensitized. This mechanism explains the seemingly paradoxical use of capsaicin as an analgesic.³⁶⁻³⁸ Vanilloid receptors are also expressed in brain regions that modulate the emotive and cognitive aspects of pain (eg, preoptic area, locus ceruleus, hypothalamus, striatum).³⁸ It has been hypothesized that modulating the expression of VR1s and their endogenous ligand (anandamide) may be one of the central mechanisms of OMT,³⁸ parallel to the potential effects of OMT on endorphins.³⁹

Needling is sometimes necessary to inactivate TrPs. For thousands of years, Chinese medicine has treated TrPs with acupuncture.⁴⁰ Travell began needling TrPs with syringes in 1942, injecting them with procaine.⁴¹ Procaine was later replaced by saline solution,⁴² which was later replaced by "dry needling"—without any fluid in the syringe⁴³—bringing the procedure full circle to what is essentially acupuncture. The "dysfunctional motor end plate hypothesis" has led to the injection of botulinum toxin, which causes an irreversible blockade of ACh release in the TrP.⁴⁴

Injecting TrPs with quinidine should be tested in a clinical trial, as quinidine decreases presynaptic ACh release (via its well-known blockade of L-type Ca^{2+} channels) and down-regulates nAChRs (a postsynaptic mechanism). In one trial, quinidine appeared to restore AChE activity.⁴⁵ Diltiazem also merits investigation. It is an L-type Ca^{2+} channel blocking agent that corrects myopathies caused by defects in AChE activity.⁴⁶

Travell and Simons recommended a diet adequate in vitamins and minerals for the prevention of TrPs.³ Supplementing the diet with phosphatidylcholine has been recommended,⁴⁷ but this may actually provoke TrPs in a portion of patients. As choline is a precursor to ACh, an nAChR gain-of-function mutation may enable choline to directly activate the mutated receptors.⁴⁸

Another new approach in treating TrPs are herbal medications. As an estimated 50% of patients with long-term musculoskeletal pain take herbal remedies, it behooves osteopathic

physicians to understand the mechanisms of these medications.⁴⁹ Herbal remedies and essential oils that are recommended for treating myofascial pain include lavender (*Lavandula angustifolia*), lemon balm (*Melissa officinalis*), rosemary (*Rosmarinus officinalis*), kava kava (*Piper methysticum*), skullcap (*Scutellaria lateriflora*), passionflower (*Passiflora incarnata*), Rose (*Rosa spp*), and valerian (*Valeriana officinalis*).⁴⁷ Nearly all of these herbs contain linalool, a monoterpene compound that inhibits end plate activity by reducing ACh release (a presynaptic mechanism) and by modifying nAChRs (a postsynaptic mechanism).⁵⁰ Marijuana (*Cannabis spp*), which also produces linalool,⁵¹ also effectively treats myofascial pain syndromes.⁵² Marijuana's efficacy may also be attributed to tetrahydrocannabinol, an N-type Ca²⁺ channel blocker.⁵³ Tetrahydrocannabinol inhibits ACh release in the CNS⁵⁴; this inhibition is thought to occur at motor end plates, as motor nerve terminals express cannabinoid receptors.⁵⁴

Conclusion

Travell and Simons' concepts regarding TrPs have converged with osteopathic medicine's concept of somatic dysfunction. This convergence is also seen in Travell and Simons' approach to the treatment of TrPs, which in many ways resembles the OMT used in Chapman reflex points,⁵⁵ Jones' counterstrain points,⁵⁶ and the progressive inhibition of neuromuscular structures (PINS) technique.⁵⁷ Armed with a better understanding of the molecular basis underlying myofascial pain syndromes, clinicians hope that Travell and Simons' approach will continue to coevolve with osteopathic concepts.

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