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NON-PHARMACOLOGIC ASPECTS OF PAIN, MIGRAINE, AND HEADACHE (D BUSE, SECTION EDITOR)

The Role of the Autonomic Nervous System in Headache: Biomarkers and Treatment

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Abstract
Purpose of Review In this review, the role of the autonomic nervous system in tension-type headache and migraine is reviewed.
Recent Findings A pathophysiological model for tension-type headache is proposed that is compatible with most physiological and behavioral literature.
Summary A treatment protocol is described that follows from this model. For migraine, incorporating autonomic factors into the pathophysiology offers rationales for behavioral interventions that have been shown to be useful in migraine treatment and a biofeedback protocol is proposed.

Keywords Headache · Biofeedback · Autonomic nervous system

The role that the autonomic nervous system (ANS) plays in headache has historically been under-valued. In this article, I review the scientific literature on the role of the ANS in migraine and tension-type headache. Recent advances in technology have spawned numerous reports on ANS function, especially parasympathetic function as measured by heart rate variability (HRV). This has allowed advances in understanding of the pathophysiology of both headache types and has led to some promising interventions.

Tension-Type Headache

"Tension-type headache (TTH) is the most common primary headache disorder with a prevalence of up to 78% in the general population and huge expenses in terms of health service. Despite its high incidence and impact on life's quality, the knowledge on the pathophysiology and efficacious treatment of TTH was still limited" (p. 793) [1, 2]. The most recent comprehensive review of prevalence [3] estimated that about 25% of males and 45% of females suffer from TTHs that are accompanied by some compromise in quality of life and productivity. Although TTH does not present the level of burden that has been found in migraine, it is far more common and thus represents a significant health challenge.

A recent review [4] concludes:

> "Despite being the most prevalent headache disorder, TTH pathophysiology remains poorly understood. Patients with TTH tend to have muscles that are harder and tender to palpation, and may have more frequent trigger points of tenderness than patients without headache. However, cause and effect of these muscular findings are unclear. Studies support both peripheral and central mechanisms contributing to the pain of TTH. Diagnosis is based on clinical presentation, while the focus of evaluation is to rule out possible secondary causes of headache. Treatment options have remained similar over the course of the past decade, with some additional studies supportive of both pharmacological and non-pharmacological options" (p. 2).

Tension-Type Headache and Autonomic Indicators

A recent review has summarized a substantial literature indicating that TTH sufferers have lower HRV indicating lowered flexibility in the ANS and specifically ventral

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medial HRV [5]. Hedges' g_s for both TTH and migraine indicated moderate effect sizes (−0.63) for both HA types, but more work needs to be done on TTH. The studies that did look at that HA type did find similar effect sizes.

Tension-Type Headache Pathophysiology

While most reviews conclude that the pathophysiology of TTH is unknown, and debate has continued on the role of peripheral versus central mechanisms of chronic TTH [6], our group has attempted to understand the pathophysiology from the perspective of peripheral pain sources that might have ANS mediation. We started from the common observation that psychological stress is universally accepted as one trigger for TTH [7–9]. The presumed pathway would then become excessive stress leading to muscle contraction and the chronically activated muscles could lead to pain. Unfortunately, the literature has not produced convincing evidence of elevated electromyographic (EMG) levels or metabolic byproducts in TTH patients when compared to controls (see, for example, [10]). In a recent comprehensive review, Ashina et al. [6] concluded: "Although the biological underpinnings remain unresolved, it seems likely that *peripheral mechanisms* are responsible for the genesis of pain in TTH, whereas central sensitization may be involved in transformation from episodic to chronic TTH" (p1, *italics mine*).

On the other hand, evidence for sensitized pain pressure thresholds is a bit more solid:

> "This first meta-analysis addressing pressure pain thresholds differences in symptomatic and distant pain free areas between patients with tension-type headache and controls found low to moderate evidence supporting the presence of pressure pain hypersensitivity in the trigeminal and neck areas in tension-type headache in comparison with headache-free controls. Sensitivity to pressure pain was widespread only in chronic, not episodic, tension-type headache (moderate evidence) [11] (p. 256)."

In recent years, myofascial trigger points (TPs) have been increasingly accepted as playing a role in TTH [6, 11–17].

Furthermore, a number of studies have found that methods of "releasing" TPs can reduce HA frequency and severity [18–22], although placebo procedures are often equally effective. Perhaps the most convincing evidence comes from the study by Gildir et al. [18] where dry needling of TPs was compared to a sham dry needling condition. The actual TP needle releases were much more effective over a 6-week period (65% reduction on the HA index vs. a 33% increase for the sham needling group).

The Sympathetically Mediated Trigger Point Spindle Model

The model presented here is that TTH is largely a peripheral phenomenon related to myofascial trigger points (TPs), and that the innervation of these TPs is predominantly mediated by alpha sympathetic fibers in the ANS. One potential hypothesis is that TPs are actually related to muscle spindles which have been shown to be autonomically innervated by these sympathetic fibers [19, 23–26]. This would offer a reasonable path for stress as a trigger for TTH.

In a series of studies, our group has attempted to test this hypothesis. In this model, psychological stress activates alpha sympathetic fibers to TPs (here hypothesized a muscle spindles). The spindles consist of intrafusal fibers called bag and chain cells. They have long been known to be the stretch receptors for muscle with afferent fibers to areas in the brain that monitor muscle position and potentially pain [27, 28]. Some studies have found 1-a afferents and unmyelinated C fibers emanating from muscle spindle [29, 30], making this capsulated structure a candidate for a peripheral source of pain typical of TTH and the typical referral pattern (first reported by Travell and colleagues) seen in TTH.

To test this hypothesis, my colleagues David Hubbard and Greg Berkoff used two needle EMG recordings, one inserted into an active trapezius TP and the second in nearby non-tender muscle [31]. As predicted, the active TP showed dramatically more EMG activity than the comparison site. In a follow-up study, two forms of pharmacological blockade were used to see if the EMG activity could be blocked by a cholinergic antagonist (curare) vs. an alpha sympathetic antagonist (phentolamine). Again, as predicted, the curare had no effect on the TP EMG activity whereas the phentolamine suppressed it almost completely and followed the time course specified for the drug half-life [32••]. This supported the model that stress leading to alpha sympathetic activation impacted TPs. We then published a number of studies that showed that various psychological stressors would dramatically increase activity in the TP, while the adjacent muscle remained quiet [33–37]. For example, in the McNulty et al. study, patients were asked to do a stressful mental arithmetic task while EMG was monitored with one probe in or near the TP and the other nearby in non-tender muscle. The TP EMG averaged 28.31 microvolts vs. the non-tender site's 4.44 microvolts. During the recovery period, the TP reduced back to its baseline of 15.99 microvolts. In all of this series of studies, the TP EMG activity proved very sensitive to stressful stimuli and in one study [38] reduced to the level of the adjacent site during a passive relaxation induction (autogenic training).

The Role of the Parasympathetic System

There has long existed well-researched concept in the autonomic physiology literature called "Accentuated Antagonism" [39–42].

Olshansky et al. [39] defined accentuated antagonism. "Vagal 'tone' predominates over sympathetic tone at rest. Under normal physiological conditions, abrupt parasympathetic stimulation will inhibit tonic sympathetic activation and its effects at rest and during exercise. This response is known as 'accentuated antagonism'" (p.863). Or from Uijtdehaage and Thayer [40], "Sympathetic heart rate effects were substantially smaller with high levels of vagal tone than with low vagal background activity. Furthermore, vagal effects became progressively stronger with increasing sympathetic background activity, demonstrating the predominance of parasympathetic control of human heart rate" (p. 107).

Thus, the parasympathetic nervous system fibers can act as a brake or governor allowing better regulation of the sympathetic input to various organs, here the TPs. We postulated that various release procedures commonly used in physical therapy and chiropractic settings (spray and stretch, acupressure, acupuncture, dry needling, etc.) produce short-term HA reductions by taking the pressure out of the TP capsule. As cited above, these interventions are usually effective, but can be short-lived. By enhancing parasympathetic tone through either various biofeedback modalities or psychological/meditative procedures, we postulated that much longer pain and pressure relief would result, presumably based on the "Accentuated Antagonism" principles cited above. This might explain the outcomes reported for Cognitive Behavioral Therapy [43] and Mindfulness-Based Stress Reduction [44]. One intervention that has been shown to specifically enhance ANS regulation is Heart Rate Variability Biofeedback (HRVB).

Heart Rate Variability Biofeedback

Starting in the late 1970s, Paul Lehrer and I began developing a type of biofeedback that we hypothesized would improve autonomic homeostasis and therefore be effective in the treatment of autonomically mediated disorders [45, 46]. Since then, this procedure, either as an adjunct to other therapies or by itself, has been found to be quite effective (see [47–49]). In several studies, we have shown that regular practice of the technique based on slow breathing can improve resting baseline levels of parasympathetic function (c.f. [50]). Some evidence exists for the efficacy of HRVB for TTH [51, 52], but much more research is clearly needed. Stepanchenko and Marchenko [52] randomized 137 adolescents (ages 13–18) into four groups: adolescents with episodic (ETTH) and chronic TTH (CTTH) who received only drug therapy vs. only non-drug therapy (HRVB), and fifth group—adolescents with CTTH who received combination of drug and non-drug therapy. Results indicated that groups of non-drug therapy in comparison with only pharmacotherapy groups had statistically more pronounced decrease in the intensity of headache, a decrease in reactive anxiety and depression level, and an improvement of the quality of life. As expected, the HRVB protocol produced an increase in indices of healthier ANS function.

The "mediational model" is shown in Fig. 1. It is proposed that HA pain (here we assume that it is a variant of muscle pain) is produced primarily by TP phenomena (we sometimes call "spindle spasm"). ANS dysfunction (usually prolonged vagal withdrawal) and physical overstretch stimuli create sympathetic input to the TP. A number of emotional or physical triggers are involved in creating vagal withdrawal and/or sympathetic activation (stress, worry, social stimuli, etc.). In a parallel model [53], we found that children with functional abdominal pain had longer periods of vagal withdrawal than asymptomatic children and when HRVB was introduced, their vagal tone improved while symptoms reduced ($r = 0.63$).

Current Clinical Model

In our current model, we propose combining HRVB (perhaps accompanied by an empirically based talk therapy) with one of the TP release procedures. The patient learns the biofeedback technique over the course of 3 to 5 weeks with required daily practice of at least 10 min. After mastery is demonstrated with physiological monitoring, the patient is instructed to use the breathing technique before, during, and after the TP release. We have found this combination effective in prolonging pain reduction dramatically and preventing TTHs in the future. We are currently investigating this specific protocol against a credible comparison procedure measuring the length of pain and pressure relief.

Migraine

Because of the severity of the symptoms and their effect on daily function, migraine has been extensively studied globally [2]. Recent efforts have focused on the central nervous system mechanisms and acute and preventive treatments for migraine [54]. While this line of research has greatly improved our knowledge of the neurological nature of the migraine, less progress has been made on behavioral aspects of prevention.

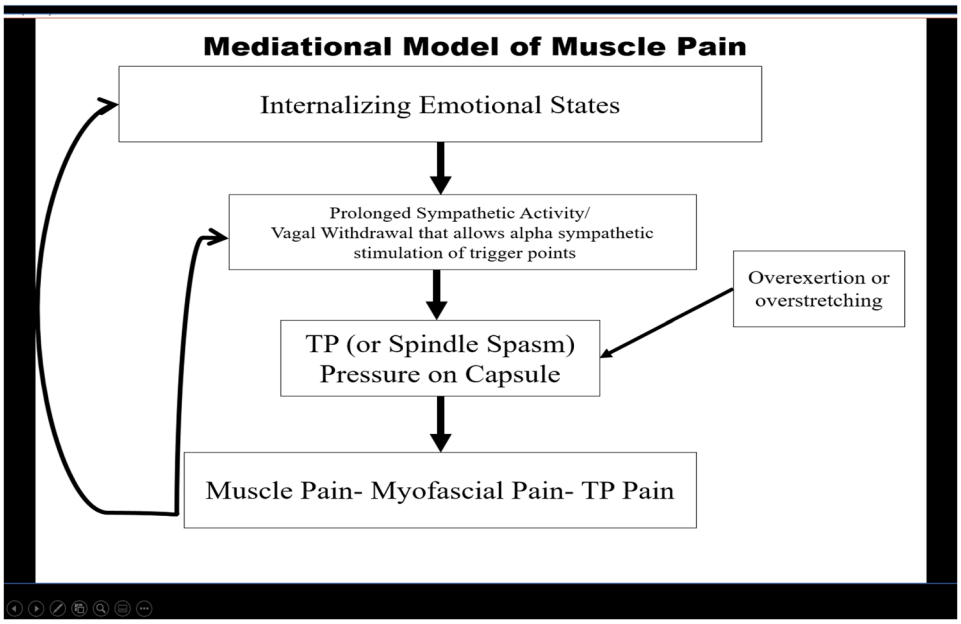

Fig. 1 A proposed model for the pathophysiology of tension-type headache

Migraine and Dysautonomia

In 2004, Peroutka [55] postulated that the ANS played a significant role in migraine. He speculated: "The amount of objective diagnostic data and clinical information indicating that migraineurs have a chronic sympathetic hypofunction is overwhelming" (p. 62). More recently [56], he summarized the existing evidence as "Migraine-related alterations in ANS function have a complex pattern, but, in general, an imbalance occurs between sympathetic and parasympathetic tone. Through an improved understanding the role of autonomic changes in pathogenesis of migraine, it may be possible to develop even more effective treatments for migraine sufferers" (p. 153). He noted that the ANS can be seen as pivotal in each aspect of migraine symptoms: nausea, vomiting, diarrhea, polyuria, eyelid edema, conjunctival injection, lacrimation, nasal congestion, and ptosis. As cited earlier, people with migraines have consistently been found to have lower HRV during the interictal and ictal periods [57].

The ANS may also be targeted for acute pain relief. In a meta-analysis, de Coo et al. [58] reported acute relief of cluster HA using vagal nerve stimulation (VNS). One study [59] also reported acute relief in migraine.

Among a number of environmental and behavioral factors, changes in perceived stress has been identified as a leading trigger for migraine attacks [60]. Based on this observation, a number of interventions targeting stress and indirectly autonomic functions have been proposed. The intervention described above, HRVB, has been shown to affect resting level autonomic flexibility and thus may be a candidate for migraine prevention.

Interestingly, in a recent double-blind, sham-controlled, random controlled multi-center trial, Diener et al. [61] examined the efficacy of a non-invasive VNS device and found reductions in HA days for both sham and actual VNS. Both groups showed gains in autonomic function. The actual VNS group that was adherent did report fewer HA days. Consistent with the idea that interventions that target ANS flexibility may be useful, in a recent meta-analysis [62], Wu et al. concluded that despite limitations in methodology, "Yoga therapy may benefit to reduce the headache frequency of migraine patients" (p. 147). One study [63] comparing a Yoga intervention to care as usual found not only reduced symptoms in the Yoga group but improved vagal tone.

Biofeedback

Biofeedback has been used for migraine treatment for many years. Many studies attempted to target the vasoconstriction/vasodilation hypotheses that were prominent earlier. Thus, modalities such as finger temperature warming and pulse volume training, often combined with relaxation techniques, were reported.

In a meta-analysis of this literature, Kisan et al. [63] found that biofeedback modalities either alone or in combination with other therapies produced treatment advantages over controls (medium effect size). The modalities included the following: peripheral skin temperature feedback in combination with relaxation training, or electromyography feedback (EMG-FB), blood-volume-pulse feedback or EMG-FB. Other studies evaluated electroencephalography

feedback, skin conductance feedback, and forehead temperature feedback. There were no differences between modalities. Nestoriuc and Martin [64], in an excellent review, summarized the literature similarly:

> "1) Various forms of biofeedback are effective for migraine and tension-type headache. 2) Outcomes with these forms of biofeedback rival outcomes with medication alone. 3) Combining biofeedback with medication can enhance outcomes. 4) Outcomes from biofeedback are similar to those obtained with other behavioral approaches. Whether biofeedback has a unique advantage over other similar approaches is not known, but at least one investigation suggests that biofeedback may be of particular value to a subset of patients. 5) Although not reviewed here, the outcome effects from biofeedback seem to endure for extended periods, whether booster treatments are provided or not. 6) Although biofeedback has been shown to be effective for a number of patients, a sizeable number of patients do not achieve significant relief" (p. s74).

A recent review and commentary in the journal *Pediatrics* emphasized the importance of non-pharmacological treatments for migraine [65]. The conclusion was that when lumping all treatments together, compared to placebos or comparison groups, non-pharmacological interventions are "… effective in treating pediatric migraine." However, few differences emerged among various modalities.

Pediatric applications using biofeedback have been reviewed recently by Koechlin et al. [66]. Five studies with a total of 137 participants met the inclusion criteria. Biofeedback reduced migraine frequency (mean difference, −1.97 [95% confidence interval (CI), −2.72 to −1.21]; $P < 0.00001$), attack duration (mean difference, −3.94 [95% CI, −5.57 to −2.31]; $P < 0.00001$), and headache intensity (mean difference, −1.77 [95% CI, −2.42 to − 1.11]; $P < 0.00001$) compared with a waiting-list control. More recently, Stubberud et al. [67] reported the results of using a smartphone-based Bluetooth device that provided information on muscle tension, heart rate, and finger temperature. A follow-up study [68] found that adherence was poor, which may have led to limited results (a one HA per month reduction in the intervention group that was not significant). Of note, the study was conducted during the early stages of the global COVID-19 pandemic which may have significantly impacted adherence.

A number of studies utilizing mindfulness interventions have been reported. In a recent review, Stubberud et al. [69] concluded that "…mindfulness may be an important tool as part of a comprehensive treatment approach to help patients 'mindfully' engage in valued life activities." (p. 217).

Based on these general findings, it appears that interventions that reduce stress or promote mindfulness-type shifts in perception can be effective adjuncts to migraine treatment, perhaps by improving autonomic function. HRVB may also be effective by directly improving autonomic flexibility (as cited above), and by improving other behavioral factors that are known to precipitate migraine (sleep, lack of exercise, rumination, impulsive behaviors, etc.). Thus far, the evidence for HRVB in migraine is limited. One recent random controlled trial [70•] found that "…an App-based HRV biofeedback was feasible and acceptable on a time-limited basis for people with migraine. Changes in the primary clinical outcome did not differ between biofeedback and control; however, high users of the app reported more benefit than low user" (p. 41). This study also had challenges with adherence which may have affected the outcomes.

Conclusions

Overall, there has emerged a general consensus that non-pharmacological interventions can add treatment gains to traditional and the newer medical treatments for headache including migraine. I have tried to emphasize the role that the ANS plays in migraine as a way of explaining the findings that a wide variety of interventions (including sham procedures and placebos) are effective in reducing HA frequency and, in a few studies, pain intensity. HRVB has been shown to improve ANS flexibility in other applications and therefore may be a promising addition to the non-pharmacological armamentarium. Future research should focus on understanding the mechanisms that seem to produce favorable results so as to improve interventions.

Compliance with Ethical Standards

Conflict of Interest The author does not have existing conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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basis for people with migraine. Changes in the primary clinical outcome did not differ between biofeedback and control; however, high users of the app reported more benefit than low users.