Curr Pain Headache Rep (2013) 17:380
DOI 10.1007/s11916-013-0380-5

MIGRAINE (R COWAN, SECTION EDITOR)

Does Exercise Make Migraines Worse and Tension Type Headaches Better?

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Published online: 15 November 2013

Abstract Many non-pharmacological treatments have been implicated in the treatment of primary headache, with exercise being a common recommendation. In this review we first provide an overview of the relationship between exercise and primary headaches. We then review the physiology of pain modulation, with focus on the endogenous opioids, endocannabinoids, and neuropeptides calcitonin gene-related peptide (CGRP) and brain-derived neurotrophic factor (BDNF), and their associations with primary headache and exercise. Finally, we summarize current literature evaluating effects of exercise on primary headache in an effort to understand the benefits and disadvantages of exercise in primary headaches.

Keywords Nonpharmacological treatment · Exercise · Migraine · Tension type headache · Primary headache

Introduction

The pathophysiologies of migraine and tension-type headache (TTH) are distinct. Several core concepts have emerged in migraine pathophysiology including cortical spreading depression, activation of the trigeminovascular system, and peripheral and central pain sensitization [1, 2]. Whereas the sensitization of peripheral myofascial pain pathways may be the most significant factor in maintaining TTH [1], this is somewhat older data that is speculative and not proven. Many physicians recommend exercise for both types of headaches and response to exercise may help distinguish migraine from TTH. Evidence remains conflicting as to the role of exercise in headache and the literature is sparse.

This article is part of the Topical Collection on *Migraine*

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Exercise and Migraine

In 1994, the International Headache Society recognized exercise-induced headaches as a primary headache diagnosis termed primary exertional headache (PEH) [3]. Defined by the International Classification of Headache Disorders (ICHD-2) as a pulsating headache, lasting from 5 minutes to 48 hours, brought on by and occurring only during or after physical exertion, PEH remains a distinct entity from migraine [4]. It can, however, have associated migrainous features such as nausea, vomiting, and photophobia. It is frequently comorbid with migraine with a study surveying 1963 adolescents reporting 47.5 % of migraineurs also having PEH. Moreover, their PEH was associated with more migrainous features and pain killer usage [5]. In this study, the most likely physical activities to induce headache were track and field, basketball, other ball games, and swimming. The actual duration of exercise, warm up and cool down from exercise, and other variables such as warm weather and low fluid intake were not documented and could all be contributing factors. How one parses the difference between a migraine with exercise as a trigger and primary exertional headache coexistent with migraine headache is not clear.

Several case reports have suggested exercise can precipitate a migraine [6–8] and a recent study suggests 22 % of migraineurs list exercise as a trigger [9]. A 1985 case report by Lambert and Burnet suggested warm-up prior to

strenuous exercise was effective in preventing exercise-induced migraine. They reported a case of a 26-year-old competitive swimmer who occasionally developed migraine after a strenuous workout without warm-up. She was instructed to do a quantitative warm up before each swim and remained headache free for 3 months. At a subsequent competition, she did not warm up and a migraine ensued [8]. However, another case report documented a 43-year-old aerobics instructor with episodic migraines with aura who successfully aborted her migraines by running during her prodromal symptoms [10]. Similarly, another case documents a 56-year-old man aborting his cluster headache with running [11]. Such case report data is difficult to interpret as headache type, frequency, comorbidities, and confounding factors may all enter into the circumstances surrounding a given patient's relationship between exercise and headache. Case reports do underscore the uniqueness of that relationship in each case.

Exercise and Tension-Type Headache

Literature on TTH and aerobic exercise is sparse. Studies in TTH headache patients have largely focused on exercises of the neck and back muscles, with stretching and posture as opposed to aerobic workouts. Several studies describe beneficial outcomes of exercise in TTH. Soderberg et al looked at group differences in chronic TTH headache patients treated with physical training, acupuncture or relaxation training. The exercise group consisted of 45 minutes of neck and shoulder exercises with warm and cool down of either ergometric bicycling or stretches. Headache intensity was reduced and headache free days increased in all groups after 6 months [12]. A secondary analysis of a randomized controlled trial in 198 office workers with likely TTH along with neck and shoulder pain showed that headache frequency decreased in both active treatment groups vs control. Intensity and duration of remaining headaches were not affected [13]. In a study looking at 1881 workers in Italy with headache as well as neck and shoulder pain, two-thirds were diagnosed with TTH and 58 % with migraine. Subjects were randomly assigned to either an intervention group consisting of head and neck postural exercises for 6 months or a control group with no intervention; both groups keeping headache diaries. Results showed an overall reduction of headache frequency and headache days per month in the physical program group [14]. A review study in 2009 evaluated 10 randomized controlled trials looking at exercise in TTH associated with temporomandibular disorder (TMD) [15•]. One cited study by Torelli et al concentrated on TTH with findings that massage, relaxation, and stretching exercise were more efficacious than no treatment in reducing headache frequency [16]. Ultimately, findings of the review suggest that postural and relaxation exercises have therapeutic value for TTH and TMD. The underlying assumption in these studies is that TTH is a structural problem, and with few exceptions, physiologic changes associated with aerobic exercise were not evaluated, nor were the effects of aerobic exercise on TTH.

Exercise Physiology and Pain Modulation in Migraine

Exercise

Physical activity is defined as any bodily movement produced by skeletal muscles, which results in energy expenditure beyond resting expenditure. Exercise, a subset of physical activity, is planned, structured, and repetitive, with the goal of improvement or maintenance of physical fitness. Aerobic exercise is any activity involving large muscle groups, is continuous and rhythmic, and moderate in intensity such as running, walking, cycling, and swimming. Intensity can be measured absolutely or relatively. Absolute intensity reflects the rate of energy expenditure during exercise, expressed in metabolic equivalents (METs), where 1 MET is a unit of sitting/resting oxygen uptake (3.5 mL O_2 per kg of body weight per minute). Relative intensity refers to the percent of aerobic power utilized during exercise, expressed as a percent of maximal heart rate, or percent of V O_{2max}. Moderate-intensity activities are those performed at a relative intensity of 40 %–60 % of V O_{2max} (or absolute intensity of 4 to 6 METs) [17, 18].

Endogenous Opioids

Since their isolation in the early 1970s the endogenous opioids, notably endorphins and enkephalins, have been implicated as mediators of pain [19–21]. Beta endorphin is an endogenous morphine-like hormone (opioid) primarily synthesized in the anterior pituitary. It is derived from a prohormone, pro-opiomelenocortin (POMC) that is the precursor molecule for various neuroactive peptides, including beta-lipoprotein, adrenocorticotropin, and variations of melanocyte-stimulating hormone. Beta-lipoprotein contains the beta-endorphin peptide exhibiting its most noted biological activity, analgesia [22]. Endogenous opioids in conjunction with serotonin (5HT) modulate spontaneous pain [23, 24]. Beta endorphin is released during painful and stressful events and stimulates presynaptic opioid receptors inhibiting the release of neurotransmitters such as noradrenaline, acetylcholine and 5HT [25].

Several studies have reported evidence of dysfunction of the endogenous opioid system in migraine. In 1980 Anselmi et al measured CSF levels of enkephalins and beta-endorphin-like-immunoreactivity (Beta-ELI) in idiopathic headache patients. CSF enkephalins were measured in 15 migraine patients during an attack, 8 patients during a headache free

period, 5 cluster headache patients, and 5 controls with results showing CSF enkephalin levels in migraine sufferers during the attack period to be significantly lower than that of the free period and that of controls. Serum samples of Beta-ELI were taken from 15 migraine sufferers at the end of an attack, 33 in a headache free period, and 10 controls with results showing levels at the end of the attack were significantly higher than headache free and control patients. The enkephalins and beta-endorphin do exercise a modulating role in the perception of pain. Thus in a condition of acute pain without evidence of peripheral motivation such as idiopathic headache or migraine, failure of this neuropeptide system controlling the pain suppressing mechanism might be involved in the pathogenesis of this disease. Endogenous opioids increase in human CSF during pain and emotional stress. On the other hand, this study showed a decrease or a complete disappearance of morphine-like substances in CSF during migraine attacks. This might suggest an intermittent repetitive failing of the enkephalinergic system during the attack in migraineurs. In addition, they suggest a correlation between hyperendorphinemia and stress provoked by the attack, with the elevation of beta endorphins at the end of the attack playing a role in attenuating the crisis and restoring the previous state of well-being [26]. In another study by Genazzani et al CSF beta-endorphin levels were measured in 2 groups of migraine sufferers with increasing severity of disease and healthy controls. The migraine without aura (MO) group had a frequency of 2–9 migraines in the month whereas the migraine with chronic daily headache (CDH) group had 8–15 migraines during the evaluated month. Beta-endorphin levels were closely correlated to the severity of the disease: they decreased significantly from those in healthy controls to those of MO sufferers to the lowest levels found in CDH patients [27]. These findings support the hypothesis of migraine as an evolutive disease linked to a deterioration of antinociceptive system, biochemically sustained by the progressive reduction of beta-endorphin levels in CSF. A more recent study by Misra et al demonstrated similar findings with plasma beta endorphin levels significantly lower in migraines patients compared with controls and lower in chronic compared with episodic migraine [28], again suggesting the spectrum of migraine in relation to endorphins.

Other groups have measured the levels of beta endorphins in circulation and other tissues. A review article by Schwarz and Kindermann in 1992 assessed the changes in beta-endorphin levels in response to aerobic and anaerobic exercise with various workload and durations. There were varied results as to whether beta-endorphins responded to exercise intensity in a systematic manner with results ranging from unchanged levels to markedly elevated [29]. For instance, De Meirleir et al investigated lactate as an intensity-related metabolic parameter and found that during incremental graded cycle ergometry at a lactate level of 3 mmol/L there was no significant change in beta-endorphin level compared with pre-exercise levels. However, at exhaustion, beta-endorphin levels increased in parallel to lactate levels [30]. Subsequent studies reported that elevation in beta-endorphin levels did not occur until the anaerobic threshold was exceeded, which corresponded to 75 % $VO_{2max,}$ and after exercise cessation [31–34]. Similarly, various studies found that high intensity, short duration, [seconds to minutes], of anaerobic exercise stimulates the release of beta-endorphin [35–39]. Beta-endorphin levels during endurance exercise have found disconcordant results, however, with some studies showing unchanged levels, whereas other demonstrating significantly increased levels[29]. Later studies looked at measuring beta-endorphin at varying degrees of intensity, during endurance exercise, ranging from 40 %–80 % VO_{2max} with a consensus that beta-endorphin increases above a workload of 70 % VO_{2max} or when an anaerobic threshold of 4 mmol/L is exceeded [29]. Furthermore, when assessing prolonged endurance exercise at a steady state of 63 % VO_{2max} or 3–3.5 mmol/L of lactate, Scwarz and Kindermann found that increases in beta-endorphin were only seen after about 50 minutes of exercise [40]. Taken together, increases in beta-endorphin are dependent not only on intensity of aerobic exercise but also on duration of endurance exercise.

Endocannabinoids

Endogenous cannabinoids or endocannabinoids (eCB) have been hypothesized to synergistically work with the opioid system in producing antinociception. Two cannabinoid receptor subtypes, CB1 and CB2, along with their naturally occurring ligands, derived from arachidonic acid N-arachdonoylethanolamide (anandamide, AEA) and 2-arachidonylglycerol (2-AG), palmitoylethanolamide (PEA), and others, have been identified. CB1 receptors are found both in the central and peripheral nervous system whereas CB2 receptors are located mainly in peripheral tissue [41–43]. In the brain, they act as retrograde neurotransmitters and are synthesized and released from postsynaptic neurons, and bind to CB1 in the presynaptic terminal. Specifically, CB1 receptors inhibit the release of neurotransmitters such as GABA, glutamate, dopamine, noradrenaline, and acetylcholine and thus have been implicated in central pain modulation and signal transmission [44]. Peripherally, a portion of analgesic effects can be attributed to the expression of CB1 receptors in primary afferent neurons, and also CB2 receptors mediating the anti-inflammatory role of eCB and contributing to local analgesia via expression in primary sensory neurons [45, 46].

A deficiency in the eCB system has been hypothesized as an underlying mechanism in migraine pathophysiology and other pain conditions [47]. Studies have shown that AEA is tonically active in the periaqueductal gray matter, thought to be a migraine generator [48] as well as in the in the trigeminovascular system where it may play a modulatory role [49].

Sarachielli et al tested the concentrations of AEA, PEA, and 2-AG as well as CGRP and the end product of NO, nitrates, in the CSF of chronic migraine, probable chronic migraine, and probable analgesic-overuse headache patients with the hypothesis that eCB system may be dysfunctional in migraine [50]. CSF levels of AEA were significantly lower and those of PEA were slightly, but significantly elevated in all headache groups compared with controls. There was also a negative correlation between AEA and CGRP in migraineurs, with a similar trend in nitrite levels. They postulated PEA levels may increase in compensation for reduced AEA in migraineurs. To investigate receptor function, Van der Schueren et al used positron emission tomography (PET) on 20 female migraineurs interictally, and 18 controls 90 minutes after intravenous injection of the radioligand [18F]MK-9470 to assess its binding to CB1 receptors [51]. Their findings of increased CB1 binding in migraineurs supports the idea of deficient eCB in these patients. Perrotta et al hypothesized that in migraine patients with MOH, dysfunction of eCB system could contribute to sensitization of trigeminal and spinal pain pathways, which had previously been observed in animal studies [49, 52–54]. They looked at the temporal summation threshold of the nociceptive withdrawal reflex, as a measurement of facilitation of spinal cord pain processing, and the platelet activity of the enzyme that degrades AEA, fatty acid amide hydrolase (FAAH), in 27 MOH subjects and 14 controls, before and 10 and 60 days after a standard inpatient medication withdrawal treatment. They found that before withdrawal treatment there was a marked facilitation in spinal cord pain processing in MOH compared with controls. Furthermore, they found a significant reduction in FAAH activity in MOH subjects at 10 and 60 days after withdrawal treatment, suggesting this could be a way to rapidly increase the availability of eCB, in turn promoting restraint of the pain processing facilitation.

The eCB system has also been implicated in the mechanism for exercise-induced analgesia. In 2003 Sparling et al evaluated serum anandamide and 2-AG levels in trained male college students; 8 running on a treadmill, 8 cycling on a stationary bike, and 8 sedentary controls immediately prior to and following an exercise session. All exercising participants showed a significant post-exercise increase in anandamide levels with a similar, but not statistically significant, increase in 2-AG. Thus, leading to the first evidence of exercise activation of the eCB system suggesting a new neurohormonal mechanism for exercise-induced analgesia and the idea of "runner's high" [55]. Raichlen et al report an increase in AEA levels in high-intensity endurance running but not low-intensity walking, in the cursorial mammals, humans and dogs, but not in the non-cursorial ferret at any intensity [56]. This implies a neurobiological reward for endurance exercise, further supporting the notion of eCB in exercise induced analgesia. A subsequent study by the same group reasserts the importance of aerobic intensity for eCB release during exercise [57]. They examined AEA levels following treadmill running in 10 physically fit participants at 4 different intensities. Results demonstrate that only moderate-intensity exercise, 70 %–85 % of age-adjusted maximum heart rate (AAMHR) correlating to a slow jog or medium-intensity run, leads to increases in circulating AEA levels compared with a moderate speed walk and high-intensity run. There were no significant changes in 2-AG levels at any exercise intensity. Overall, these studies demonstrate exercise activation of the eCB system in a narrow window of exercise intensities.

Calcitonin Gene-Related Peptide (CGRP)

CGRP is a 37-amino acid neuropeptide first identified in 1983 in rats and 1 year later in humans. It is derived from the gene encoding calcitonin by alternative splicing of mRNA and proteolytic processing of its precursor. CGRP occurs in 2 isoforms, alpha and beta-CGRP, with the alpha isoform predominating in sensory neurons [58•]. CGRP is widely distributed in the central and peripheral nervous system where it is involved in vasodilation and sensory transmission. In theories of cortical spreading depression migraine is thought to be secondary to cerebral oligemia due to neuronal dysfunction, subsequently followed by a reflex painful vasodilatation of cranial blood vessels. Nociceptive information from the blood vessels is conveyed to central neurons in the trigeminal sensory nucleus that modulate pain signals to higher centers where pain is perceived. Additionally, stimulation of trigeminal nerves may also release CGRP thus reinforcing already existing vasodilatation and relaying nociceptive impulses to the CNS [59].

In 1995 Gallaie et al reported CGRP levels were elevated in venous blood during a migraine attack, but did not differ from controls in the headache free period [60]. In 2002 Goadsby et al found that plasma concentrations of CGRP in jugular venous blood but not other neuropeptides were elevated during the headache phase of a migraine attack [61]. On the other hand, Ashina et al described increased levels of venous CGRP in migraineurs outside of attacks [62]. Moreover, other studies demonstrated a strong correlation between plasma CGRP concentrations and migraine headache; that baseline CGRP levels were significantly higher in migraine patients; IV infusion of CGRP produced migraine-like headaches and changes in plasma CGRP levels during migraine attacks were significantly correlated with headache intensity [58•]. A study looking at CGRP and cerebral blood flow suggests there may be various mechanisms to CGRP induced migraine. IV CGRP or placebo was studied in 12 patients with migraine. There was no change in regional cerebral blood flow (rCBF) at the end of CGRP infusion compared with control, and the flow velocity of the MCA was decreased in the CGRP group. Since rCBF was unaffected, this indicates MCA dilation. However, this effect was so small, that

CGRP induced vasodilation was deemed unlikely to be the sole mechanism of CGRP-induced migraine [63].

Studies have shown conflicting results regarding changes in CGRP after exercise. It is theorized that in conditions of sympathetic activation with vasoconstriction such as migraine, and subarachnoid hemorrhage, the sensory nerve fibers from which CGRP and Substance P are released may act as a counter-regulatory balancing system. In 1995, Lind et al sought to determine levels of CGRP in exercise-mediated activation of the sympathetic nervous system. They found that CGRP increased progressively during exercise, whereas substance P increased after, but not during, exercise. They concluded that CGRP was released simultaneously with other sympathetic vasoconstrictors such as noradrenaline and neuropeptide Y to serve as a counter regulatory mechanism against vasoconstriction [64]. Scifter et al also looked at CGRP levels during exercise [65]. In 9 male endurance runners who were tested at different intensities of training and at rest, CGRP increased with exercise regardless of the training condition. Hasbak et al investigated the effects of hypoxia and exercise on CGRP levels and found no change in resting CGRP levels during hypoxia but a significant decrease in CGRP during exercise in a hypoxic state [66]. However, they found no correlation with the release of noradrenaline. In using microdialysis to measure CGRP from muscles Jonhagen et al reported a significant increase in CGRP detectability after eccentric exercise. They postulated that this increase in CGRP may be associated with the increased experience of pain in delayed onset muscle soreness [67].

Brain-Derived Neurotrophic Factor (BDNF)

BDNF is a member of the neurotrophin family, a group of structurally related polypeptide growth factors that also includes nerve growth factor (NGF). In addition to its influence in neuronal development and differentiation, BDNF plays a substantial role in modulation of pain signaling [68], which is mediated by the tyrosine kinase B (TrkB) receptor. Binding of BDNF to the TrkB receptor leads to an aggregation of numerous adaptive proteins that subsequently activate several kinase cascades and intracellular transduction pathways [69]. BDNF is expressed in trigeminal ganglion neurons where its release is induced by inflammatory stimuli from various vasoactive mediators including CGRP and affects synaptic plasticity in the trigeminal nociceptive pathway [70, 71].

Various studies have evaluated the relationship between BDNF and primary headache patients. In 2005 Blandini et al evaluated peripheral levels of BDNF and NGF in primary headache patients' interictally and in healthy controls [72]. Platelet and plasma levels of BDNF and NGF were significantly lower in patients with migraines (with or without aura) and in cluster headache, although NGF was low only in migraineurs. Peripheral plasma levels in all headache groups and controls were not altered, although there was a trend towards increased BDNF in migraine with aura patients. In 2010 Tulio et al studied serum levels of BDNF during an episodic migraine attack and in the headache free period in 9 patients [73]. BDNF levels were higher statistically during episodic migraines than in headache free periods. Fischer et al found similar results with BDNF levels in migraine and cluster headaches elevated during migraine attacks in comparison with headache-free intervals. They were also statistically higher than in patients with tension type headache and controls [74]. Moreover, Sarachielli et al found that chronic daily headache (CDH) patients with previous episodic migraine had significantly higher levels of BDNF, NGF, and glutamate compared with controls. They also noted a significant correlation between BDNF and NGF suggesting that upregulation of BDNF by NGF centrally plays a key role in long-term sensitization in CDH patients. They hypothesized that other chronic pain conditions such as Fibromyalgia syndrome might be sustained by mechanisms of central sensitization and could be characterized by these same neurotrophins [75].

A recent review by Nugraha et al highlighted the role of BDNF in Fibromyalgia syndrome (FMS) patients as a key mediator in sensitized states [76]. Several studies have reported increased levels of serum, plasma, and CSF BDNF in FMS compared with healthy controls [77–79]. In a rat model of acute pain, an increase in BDNF in dorsal horn cells was found after complete Freund's adjuvant injection, whereas a decrease in BDNF expression was observed in the hippocampus [80]. In chronic pain models, increased BDNF levels were found in the frontal cortex [81]. In acute pain states up-regulation of BDNF may be interpreted by the body as an antinociceptive and protective strategy, and a malfunctioning of this system leading to continuous expression of BDNF, may be related to chronic pain states.

BDNF has as an essential role in neuroplasticity. Physical activity, especially acute exercise and training, are key triggers by which neurotrophins mediate energy metabolism and consequently neural plasticity [82]. Animal models have shown increased levels of BDNF mRNA and protein in the hippocampus after voluntary exercise in rats [83, 84] Upregulation of TrkB receptors in the hippocampus of mice in treadmill exercise group has also been shown [85]. Numerous studies in humans have reviewed the effects of physical exercise on peripheral BDNF levels. A review article by Coelho et al summarized the effects of exercise in the elderly [86•]. Five randomized control trials and 1 non-randomized control trial were included. Four studies utilized aerobic training programs, 1 implemented a single acute aerobic exercise, and 1 employed strength training. Five studies presented positive effects of physical exercise on BDNF; 3 displaying significant increases in BDNF, 1 showing significance only in male participants, and 1 demonstrating a tendency towards increased BDNF after exercise. A recent review article by Huang et al maintains similar findings [87].

This review included several articles looking at various types of exercise including acute aerobic exercise, chronic aerobic exercise, and strength training. Fifteen studies investigated acute aerobic exercise, and despite using heterogeneous exercise protocols, results were relatively consistent with 14 studies demonstrating significantly elevated peripheral BDNF in response to acute exercise. Two of these studies suggested the magnitude of BDNF increase may be dependent on exercise intensity. Six studies evaluated chronic aerobic exercise with durations of exercise ranging from several weeks to 1 year. Four reported an increase in BDNF after endurance training. Seven studies examined the effects of strength training with only 2 uncontrolled studies resulting in increases in BDNF after exercise. Another study by Schidt-Kassow et al suggests high intensity physical activity was required to elevate serum BNDF concentrations [88]. Overall, findings support the notion of increased peripheral BDNF in acute and chronic exercise, a possible dependence on exercise intensity, and little change in response to strength training.

Discussion and Conclusions

That a complex relationship exists between headache syndromes and exercise is clear. Less clear are questions of causality and pathophysiology. The same neuromodulators that influence migraine are also influenced by exercise. It is beyond the scope of this review to offer a comprehensive theory of the interplay between the biochemistry of exercise and the pathological processes operant in primary headache syndromes. However, several broad impressions do emerge from the studies summarized here: there are demonstrable differences in the way migraineurs respond to aerobic exercise during their headaches (and perhaps just before—in the "primed" state) and there is more than a suggestion that migraineurs do, in fact, process the changes brought on by aerobic activity differently than non-migraineurs or migraineurs when they are inter-ictal.

Working synergistically in endogenous pain modulation, the endorphins and eCB systems may simultaneously play a role in dysfunction of acute headache pain processing and chronic central sensitization. Enkephalin levels were found to be decreased in acute migraine attacks with hyperendorphinemia at the end of the ictal phase suggesting a failure of the enkephalinergic system and a compensatory rise in endorphins secondary to stress on the system to restore baseline [26]. Both systems show similar trends interictally in headache patients and exercise. There appears to be a spectrum of serum and CSF beta-endorphin levels in migraineurs, with low levels found in episodic migraine and even lower levels in CM compared with healthy controls [27, 28]. Aerobic exercise at moderate intensities or prolonged endurance exercise has been shown to increase endorphin levels [29–39]. Moreover, Kosegoglu et al found a beneficial effect of exercise on migraine especially in patients with lower basal beta endorphin levels [89]. Similarly in CM and MOH CSF AEA levels were reduced [50] and AEA degradation by FAAH was reduced after MOH patients underwent inpatient medication withdrawal [52]. In relation to exercise there is also a narrow window of moderate intensity aerobic exercise reported to increase eCB levels [55–57]. The failure of these 2 systems in migraineurs has potential to be mitigated by moderate aerobic exercise regimens in migraine prevention by restoring the aberrant balance of endorphins and eCB. Future studies should evaluate endorphin and eCB levels in migraineurs undergoing long-term aerobic exercise programs to see if chronic deviances in the endorphin and eCB systems are correctable via exercise.

The relationship between CGRP ictally, inter-ictally and chronically in migraineurs remains elusive. Ictally, a majority of studies demonstrate an increase in CGRP levels, and studies also suggest elevated CGRP levels migraineurs during headache free periods [60–62]. CGRP has also been shown by Lassen et al to induce delayed migraine attacks after infusion in 3 out of 9 migraineurs. Immediate mild headache was observed in 8 of the 9, while delayed headache, 1 to 12 hours later, was experienced by all, with 3 meeting criteria for migraine [90]. A more recent study from the same group revealed a dilation of the middle cerebral artery in migraineurs infused with CGRP interictally, but effects too small to be likely the only mode of CGRP induced migraine. CGRP likely acts in concert with other molecules and by other mechanisms to facilitate migraine, possibly explaining why only 30 % of migraineurs experienced migraine after infusion [67]. Furthermore, progressively elevated levels of CGRP have been demonstrated during exercise as well as increases at various workout intensities. Thus, there may be a threshold reached that activates exercise induced headaches mediated by CGRP. Chronically elevated levels combined with acute increases during exercise may synergistically precipitate migraine. This could suggest the somewhat delayed onset in headache in migraineurs during exercise - varying from minutes to hours in relation to a CGRP threshold. However, further studies on this association are warranted. It remains to be seen whether a CGRP antagonist given to migraineurs prior to exercise will alleviate exercise-induced headaches.

During migraine attacks, BDNF levels are elevated. However, during headache free periods of episodic migraineurs BDNF levels show more conflicting results [72–75]. Chronic headache patients show a consistent increase in BDNF levels [75] Animal studies suggest a dose dependent effects of BDNF. Analgesia has been noted after intracerebroventricular administration of BDNF in neuropathic pain models, whereas in neuropathic pain models allodynia has been mediated by BDNF [91, 92]. Fischer thus hypothesized; low BDNF levels may cause hyperalgesia while higher levels may induce analgesia. Further , the co-expression of BDNF with CGRP in

trigeminal ganglion neurons may cause induction of BDNF release by CGRP in vitro; an effect reversed by a CGRP-receptor antagonist [70, 93]. Similarly increased BDNF mRNA and protein was found in animal models after physical exercise [83, 84]. Several studies in humans have found increased BDNF levels after acute and chronic exercise. High intensity exercise was only found to induce elevated BDNF in a study by Schmidt-Kassau et al with successive decrease after 15–20 minutes of exercise [88]. It is possible that acute release of BDNF in conjunction with CGRP modulates migraine pain during exercise. However, in physically conditioned with longstanding exercise, BDNF may serve in antinociception. It remains to be seen if a CGRP antagonist will result in headache freedom prior to exercise induced migraines or if BDNF levels in migraineurs vary with acute and chronic exercise.

Studies looking specifically at the effects of exercise on migraine suggest positive outcomes, especially in migraine-associated disability. Lockett and Campbell looked at the effects of 6 weeks of aerobic dance and calisthenics in 11 women vs 9 wait-list controls [94]. There was a statistically significant decrease of perception of migraine pain based on the Pain Severity scale as well as trends towards reduction on the Affective Distress scale and in the frequency, intensity, and duration of migraines. A more recent study looked at the effects of aerobic indoor gymnastics in 15 women and 15 control participants. They found a significant reduction of self-rated migraine pain intensity, however, no significant difference was noted in ratings of migraine frequency and thinking about pain [95]. Another study reported that regardless of the physical exercise modality, aerobic or strength training, in medical students, there was a reduction in functional disability of migraines, measured by the MIDAS scale, in students that exercised [96]. Migraine and depression are frequently comorbid [97] and physical activity has been associated with decreased depressive symptoms [98]. Exercise may have a similar mechanism of action as an antidepressant and analgesic or provides an increased overall sense of well-being. This may provide the migraineur a sense of control over their own pain intensity or serve as a distraction from a heightened awareness of pain.

Moreover, there is good evidence that sub-maximal aerobic activity can be protective and there is at least the suggestion that migraineurs can develop a "tolerance" to the pain-inducing effects of moderate exercise through careful warm-up and graded exercise programs. Busch and Gaul reviewed the data in 2008 investigating 8 studies and 4 case reports looking specifically at migraine headaches and aerobic exercise. Exercise averaged 2–3 times a week for 20–60 minutes, averaging 11 weeks, with warming up and cooling down integrated in only 4 studies, V02 max measured in only 3, and fitness coach supervision in only 3 studies [99•]. In the study by Narin et al there was a significant, greater than 50 % reduction, in headache days after 8 weeks [100]. The study by Grimm et al reported decreased number of migraine attacks but did not offer statistical data [101], and the study by Koseoglu et al found a reduction from 2 to 1 of migraine attacks per month in the exercise groups [89]. Gerber et al found a significant reduction in migraine frequency and pain intensity in the second course of intervention, the last 6 weeks of the study [102]. The other included studies did not report significant changes in headache frequency with exercise. Overall, the majority of studies did not find a significant reduction in headache attack or duration, but did indicate a reduced sensation of pain intensity. A recent randomized controlled study looked at the effects of 40 minutes of aerobic exercise 3 times a week for 3 months vs topiramate and relaxation as controls. There was a mean reduction in migraine attacks in the exercise group and the relaxation group and the topiramate group suggesting that exercise may be an option for the prophylactic treatment of migraines in patients who are unable to tolerate or did not benefit from medication [103].

While the complexities of the biochemical relationship between exercise and pain in general is just beginning to be understood, it seems safe at this juncture to incorporate moderate, graded aerobic exercise into treatment strategies for primary headache, whenever possible. At the same time, there is sufficient evidence to recommend avoidance of moderate exercise during a migraine attack, despite anecdotal reports of an abortive benefit. The relationship between exercise and pain, particularly migraine would seem a rich area for further exploration of both the pathophysiology of migraine and the therapeutic benefits of exercise in patients with chronic pain.

Compliance with Ethics Guidelines

Conflict of Interest Nada Ahmad Hindiyeh declares that she has no conflict of interest. John Claude Krusz declares that he has no conflict of interest. Dr. Robert Cowan serves as a Section Editor for Current Pain and Headache Reports.

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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