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Increasing Neuroplasticity to Bolster Chronic Pain Treatment: A Role for Intermittent Fasting and Glucose Administration?

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Abstract

Neuroplastic changes in brain structure and function are not only a consequence of chronic pain but are involved in the maintenance of pain symptoms. Thus, promoting adaptive, treatment responsive neuroplasticity represents a promising clinical target. Emerging evidence about the human brain's response to an array of behavioral and environmental interventions may assist in identifying targets to facilitate increased neurobiological receptivity, promoting healthy neuroplastic changes. Specifically, strategies to maximize neuroplastic responsiveness to chronic pain treatment could enhance treatment gains by optimizing learning and positive central nervous system (CNS) adaptation. Periods of heightened plasticity have been traditionally identified with the early years of development. More recent research however has identified a wide spectrum of methods that can be used to "re-open" and enhance plasticity and learning in adults. In addition to transcranial direct current stimulation and transcranial magnetic stimulation, behavioral and pharmacological interventions have been investigated. Intermittent fasting and glucose administration are two propitious strategies, which are non-invasive, inexpensive to administer, implementable in numerous settings, and may be applicable across differing chronic pain treatments. Key findings and neurophysiological mechanisms are summarized, providing evidence for the potential clinical contributions of these two strategies toward ameliorating chronic pain.

Keywords

chronic pain treatment; intermittent fasting; glucose supplementation; neuroplasticity; non-invasive interventions

I. Neuroplasticity and chronic pain

Changes in the brain are well documented in response to chronic pain, particularly in regions involved in affective and somatosensory processing [4;6;11;29;31]. Systematic changes in

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brain structure and function include a decrease in gray matter and white matter integrity, alterations in neurotransmitters, and decreased descending inhibition [6]. Consistent with current diathesis-stress models of pain, evidence suggests that pre-existing vulnerabilities interact with pain-related input [5;45]. Changes are positively associated with duration, intensity, and pain-related learning and memory which facilitates the maladaptive plasticity [4;11]. Essentially, the brain becomes an expert in pain. There is no question that the complex array of brain changes in response to chronic pain poses a challenge when it comes to developing and implementing effective treatments [6]. Importantly, encouraging evidence suggests that alterations in the brain associated with chronic pain are modifiable and reversible with effective clinical interventions [9]. In order to counteract the maladaptive plasticity associated with chronic pain, pairing pain treatment interventions with strategies that can increase neuroplasticity and optimize the brain's ability to learn, adapt, and implement new information may improve treatment outcomes.

Periods of heightened plasticity extend across the lifespan but are predominant in the early years of development [8;17]. Although the adult brain is capable of adapting to new experience, numerous factors associated with aging reduce the efficiency of new learning, such as changes in excitatory/inhibitory balance, myelin formation, receptor expression, and changes in neuroendocrine regulation [17;21]. Strategies to maximize neuroplastic responsiveness to chronic pain treatment could enhance treatment outcomes by increasing plasticity and synaptogenesis [8;17], thereby increasing learning and positive central nervous system adaptation.

There have been a number of investigations combining behavioral treatment strategies with the plastic benefits of pharmacological interventions [17]. For example, fluoxetine and D-cycloserine both have neuroplasticity-promoting properties. Fluoxetine was used to enhance the effectiveness of physiotherapy in stroke patients resulting in greater motor recovery over a three month period compared to placebo [7]. Fluoxetine has also been investigated as an intervention in preclinical studies to improve plasticity in the adult visual cortex thereby increasing visual acuity in adult amblyopic eyes (i.e. lazy eye), clinical investigations are in process [17;30]. Another example is D-Cycloserine which has been shown as beneficial in enhancing the effects of exposure-based therapy in the treatment of anxiety disorders [39]. Likewise, chronic pain treatment might be optimized by pairing treatment interventions with strategies that will facilitate neurobiological responsiveness, increasing adaptive neuroplasticity and improving learning and memory retention.

II. Strategies to enhance neuroplasticity

Over the past decades, animal and human research has identified multiple techniques that can "re-open" and stimulate neuroplastic responsiveness in the CNS [8;17]. In addition to the pharmacological strategies described above, transcranial stimulation methods such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) also facilitate plastic changes [12;20]. The plastic changes from transcranial stimulation methods are perceived to result from activating a combination of excitatory and inhibitory neurons in specific and select cortical regions of the brain. The transcranial stimulation methods are frequently paired with tasks designed to selectively activate particular networks,

thus facilitating and amplifying learning processes [8]. However, there are a number of limitations to the use of transcranial stimulation methods for intervention. Both TMS-based and tDCS-based interventions are not widely available and require advanced technical knowledge. Additionally, they require expensive equipment and specialized training of personnel, have limited portability, and tDCS is still being refined and improved in terms of specificity and safety as the underlying mechanisms are not yet fully established.

Importantly, similar neuroplastic changes can be activated through even less invasive interventions, such as behavioral and lifestyle strategies, including exercise, incremental training, educational video games, caloric restriction, and intermittent fasting [17;46]. Many of these techniques could be applicable to chronic pain populations. The benefits of environmental enrichment are becoming more recognized in preclinical and clinical pain research [6]. Although exercise is not a new consideration in chronic pain treatment, the increasing recognition of its neuroplastic benefits provides further incentive [26;46]. Nonetheless, adherence to a regular exercise program represents a significant barrier to successful implementation, particularly for individuals who are living with chronic pain [2].

Effective neuroplastic interventions that are non-invasive, and reasonable to implement and maintain would represent a significant clinical asset in the treatment of chronic pain. The present article focuses on two promising interventions with the potential for general application: intermittent fasting and glucose administration. This paper will present the evidence regarding the neuroplastic and learning-related benefits, the plausible mechanisms, and the opportunities for clinical application of intermittent fasting and glucose supplementation as strategies to bolster chronic pain treatment.

III. Potential Partners to Bolster Pain Treatment

Caloric restriction and intermittent fasting confer numerous health benefits including extending the life span, postponing the onset of age-related diseases, delaying or preventing age-related brain function deficits, increasing visual cortex plasticity, and improving cognitive functioning [13;25;41]. While long-term maintenance of caloric restriction is challenging, intermittent fasting appears to provide a competitive alternative that is more realistic to implement [3]. Intermittent fasting regimens can produce benefits with fasting periods as brief as 16 –24 hours [18;19;27]. Preclinical and clinical studies have reported multiple adaptive changes following intermittent fasting [28]. From a cellular perspective, intermittent fasting promotes improved cellular functioning by way of reducing inflammation and oxidative stress and increasing cellular metabolism [23]. Neurobiologically, intermittent fasting increases synaptic plasticity and can stimulate production of new neurons from neuronal stem cells [28]. In the area of performance, improvements in sensory and motor functioning and learning and memory have been observed [23]. Clinically, intermittent fasting can attenuate maladaptive age-related processes and diseases, including reductions in obesity, hypertension, and rheumatoid arthritis [23]. As such, intermittent fasting may not only enhance the effectiveness of pain treatment interventions at a functional and mechanistic level but may also confer a number of health-related benefits including promoting overall health and may contribute to a decrease in pain experience via a reduction in central and peripheral inflammation.

Although clinical trials implementing various schedules of interment fasting are few, the findings and adherence thus far have been positive [18]. Horne and colleagues investigated acute biological changes in response to a one-day, water only fast in healthy adults (ages 19 to 64) [19]. Even with the brief fasting period, significant changes were observed in metabolic, cardiovascular, and general health biomarkers. While such acute changes may contribute to reduced health risk and improved functioning, prospective investigations are needed to determine possible longer-term benefits [19]. A second study evaluated the efficacy of intermittent fasting (twice a week) and a 300–500 kcal reduction daily for the rest of the week for three months on quality of life in men who were an average age of 59 [44]. Participants were excluded if they had mental or physical disabilities and were randomized to an intervention (n= 12) or control group (n= 13). Adherence was promoted with individual/group counseling, weekly phone contact, and tracking logs. Although the sample size was small, there were no adverse outcomes or difficulties adhering to the protocol. Improvements in body composition, vitality, and lower levels of pain were reported in the intervention group compared to controls [44]. A third study compared calorie restriction to intermittent fasting in 107 premenopausal, overweight or obese women over a six-month period [15]. Participants were stratified by a number of factors and then randomized to a 25% calorie restriction 7 days a week or an intermittent fasting, 25% calorie intake (75% restriction) for two days (48 hours) a week. Some mild adverse effects were reported by the intermittent fasting group such as low energy, headaches, and constipation. A total of 18 participants withdrew but did not differ by group. Both groups showed comparable weight loss as well as similar reductions in metabolic, inflammatory and endocrine biomarkers [15]. In review of these three studies, biological changes and physiological benefits were indicated with intermittent fasting and comparable to caloric restriction. Mild adverse events were reported for 48 hours of fasting but not for the 24 hour periods. Adherence across studies was adequate to good. Two studies included 48 hours of fasting weekly, one study involved two 24 periods on separate days of the week [44] and the other a 48 hour period of fasting [15]. Participants in the 24 hour, twice a week protocol reported minimal difficulties compared to the individuals in the 48 hour period where mild experiences of discomfort were indicated. Future studies may want to explore the minimal dose and frequency of intermittent fasting that would promote functional gains, while still being reasonable to implement and sustain (e.g., 16 to 24 hours of fasting, ranging from once a month to twice a week) [18;44].

In regard to risk, extended periods or excessive fasting may have significant side effects e.g., excessive weight loss, anemia, diarrhea, malnutrition, dysregulated eating behaviors, organ damage, poorly functioning immune system [18]. Preclinical findings further endorse the risk with adverse cardiac effects demonstrated in a prolonged, 6 month, alternate day fasting schedule [1]. However, intermittent, brief, and occasional fasting periods have been shown as tolerable and safe, with possible mild side effects such as headaches, lightheadedness, and hunger sensations [18;34]. Adequate hydration should be encouraged during fasting periods to help reduce hunger pangs and promote optimal functioning [18;19]. Concerns of intermittent fasting stimulating dysregulated eating patterns have been raised, but such effects have not been reported [15;18]. In general, individuals who should be excluded from intermittent fasting interventions would include children, pregnant women, and those

diagnosed with diabetes and eating disorders [18;34]. Some studies have also excluded individuals with a history of myocardial infarction, peripheral vascular disease, stroke, immunodeficiency, organ transplant in past year, mental health or substance abuse disorders, or current cancer treatment [15;18;19].

Another learning and neuroplastic enhancement strategy warranting investigation in chronic pain treatment is glucose administration. With over 30 years of research, there is ample evidence that glucose administration improves memory in animals and humans [32]. The "glucose memory facilitation effect" has been demonstrated in older adults; healthy, young adults; and adults with various neurocognitive deficits [40]. A decrease in glucose metabolism is a byproduct of aging and is associated with poor cognitive functioning [21;32]. Glucose administration promotes improved verbal episodic memory, attention, working memory, visuospatial functioning and memory, hippocampal-related contextual learning, and retrieval processes [14;21;40]. Neurobiologically, glucose supplementation produces enhanced activation in the hippocampus, prefrontal cortex and increased functional connectivity between the hippocampus and the amygdala [37]. Interestingly, glucose ingestion activates central dopaminergic reward pathways [10], which have been implicated in chronic pain [35]. Thus, glucose administration can promote improved cognitive functioning and increased neuroplasticity, which may enhance pain treatment effectiveness via its impact on learning and memory and through the activation of important pain-related brain pathways.

Understandably, there may be some hesitation regarding providing a glucose supplement when obesity is a prevalent issue in chronic pain. First, the amount of glucose required to enhance neuroplasticity, within the range of 25–50 grams [40], is equivalent to eight to sixteen ounces of orange juice. Second, there is evidence that the consequences of glucose consumption differ from fructose consumption. Specifically, in a comparison of consumption of glucose and fructose-sweetened beverages in older, overweight and obese adults over a period of ten weeks, consumption of fructose-sweetened beverages was associated with increases in adiposity, dyslipidemia, and a decrease in insulin sensitivity compared to individuals consuming the glucose-sweetened beverage [42].

Numerous studies have investigated the cognitive benefits of glucose supplementation in adults of all ages. The effect of glucose supplementation on episodic memory was investigated in a counterbalanced cross-over design. Twenty adults, an average of 69 years of age completed an overnight fast and then consumed either 25mg glucose or a saccharin placebo. Blood glucose was measured at three time points (baseline, and 17 and 55 minutes post ingestion). Findings indicated that glucose administration enhanced episodic memory and changes in blood glucose levels at 17 minutes post-ingestion from baseline were inversely associated with memory/cognitive performance [38]. In a second study, young healthy participants consumed 25 g of glucose or placebo following a two hour fast. Glucose administration enhanced performance on a recognition memory task, particularly the measure of episodic memory, though blood glucose levels did not predict memory performance. The authors interpreted the findings as suggesting that glucose may specifically enhance memory responses that are mediated by activation of the hippocampal system [43]. In a study of younger (n = 24) and older adults (n=24), glucose administration

was compared to placebo specific to recognition memory and single/dual task conditions. Participants consumed 25 g of glucose or a saccharin placebo following a 12-hour water fast. Glucose consumption enhanced recognition memory speed and task performance in the older adults only [24].

Across studies, glucose has a memory facilitation effect, particularly in older adults and glucose regulatory factors may be more relevant to memory functioning in older versus younger adults. In general, a dose of approximately 25 g following a 2-hour water fast appears sufficient. Higher doses may be needed if glucose supplementation follows a 12-hour water fast [36]. Further investigation regarding dosing is needed, particularly when assessing the possible memory enhancing and neuroplastic benefits of pairing glucose administration with chronic pain treatments. Interestingly, Macpherson and colleagues point out that the hyperglycemia associated with metabolic syndrome and Type-2 Diabetes is associated with decreased rather than improved cognitive functioning. They offer that the discrepancy may be explained by differences in chronic versus transient increases in glucose [24]. Finally, typical exclusion criteria for glucose administration studies include neurological and psychological/psychiatric conditions, diabetes, and chronic hypoglycemia [33;43]. Assessing for elevated fasting glucose and/or impaired glucose tolerance should also be considered [24].

IV. Mechanisms

There are a number of underlying mechanisms whereby intermittent fasting and glucose administration may enhance neuroplasticity. Comprehensive reviews are published on both strategies [22;23;26;28;40]. As such, a brief summary of key mechanisms will be presented for each. Intermittent fasting activates a short-term corticosterone increase, ketones (alternative energy source from the liver) are released into the bloodstream, there is a decrease in GABAergic inhibition, and an elevation in histone acetylation rates [41]. While reduction in meal frequency induces mild metabolic stress, it also reduces accumulation of oxidative stress on neurons caused by free radical oxygen molecules, and increases in protein chaperones and neurotrophic growth factors including brain-derived neurotrophic factor (BDNF), which exerts positive effects on neuronal survival and synaptogenesis [28;46]. Additionally, circulating factors such as insulin, IGF-1, pro-inflammatory hormones and cytokines are decreased and anti-inflammatory hormones and cytokines are increased [46]. Interestingly, given that chronic pain can be experienced as a chronic stressor [5], the question might arise as to the benefit of adding another mild stressor to the system. Preclinical research indicates that corticosteroid receptor expressions differ in situation of uncontrollable stress compared to the mild stress of diet restriction. Additionally, chronic stress is associated with decreases in BDNF compared to the increased BDNF levels observed with diet restriction [28].

The mechanisms underlying the neurocognitive benefits of glucose administration have been postulated to involve the hippocampus and include glucose, insulin, acetylcholine (ACh), and adenosine triphosphate-sensitive potassium channel (K_{ATP}) regulation [22;37;40]. With oral administration, glucose is able to cross the blood-brain barrier and extracellular glucose is more readily available to replenish hippocampal deficits [37;40]. Insulin receptors are

predominant in the hippocampus and insulin levels increase with glucose administration and are positively associated with cognitive functioning [40]. ACh is a neurotransmitter with a role in memory encoding and facilitating selective excitatory and inhibitory functions [16]. An increase in brain glucose facilitates an increase in hippocampal ACh synthesis, which is associated with improved cognitive performance [21;37;40]. Lastly, glucose may increase cognitive performance by regulating activity of K_{ATP} channels [40]. Higher levels of brain glucose are associated with lower K_{ATP} channel activity. Blocked K_{ATP} channels are associated with increased cognitive performance and increased neuronal excitability [22;37]. An essential component of plasticity is synaptic excitatory and inhibitory (E/I) balance [17]. With aging the E/I balance becomes dysregulated or imbalanced [17]. Both intermittent fasting and glucose administration appear to contribute toward optimizing the E/I balance via differing pathways.

V. Implications and Future Directions

Initial attempts towards leveraging preclinical research on neuroplasticity for improving clinical treatment outcomes are promising [8;17]. Chronic pain is a central nervous system condition that is maintained by maladaptive neuroplastic changes in structure and function, which heretofore have been inadequately addressed in most forms of chronic pain treatment. There is encouraging evidence however that pain-related changes are modifiable and reversible with effective clinical treatments [9]. By combining neuroplastic strategies with chronic pain treatment, neurobiological responsiveness might be enhanced resulting in increased adaptive plasticity contributing toward improved learning, memory, and function. A comprehensive array of strategies has been identified that facilitate synaptic plasticity and neurogenesis, some of which have been successfully coupled with clinical treatment interventions for various conditions [8;17].

There is strong evidence that glucose administration and intermittent fasting are useful methods to promote synaptic plasticity and learning. Compared to other neuroplastic enhancement techniques, intermittent fasting and glucose administration represent some of the least invasive with the lowest risk. Both strategies are inexpensive to administer, implementable in numerous settings, and may be applicable across a wide range of chronic pain treatment modalities including cognitive, behavioral, pharmacological, and physical therapy. Additionally, the interventions themselves may extend beyond neuroplastic benefits and promote improved general health and cognitive functioning, contributing to an improved quality of life for individuals living with chronic pain (Figure 1). Thus, the first step is to determine if intermittent fasting and/or glucose supplementation is effective in bolstering chronic pain treatments. If the findings are affirmative the next steps would include investigating optimal dosage and delivery methods specific to different pain conditions and in conjunction with different treatment modalities.

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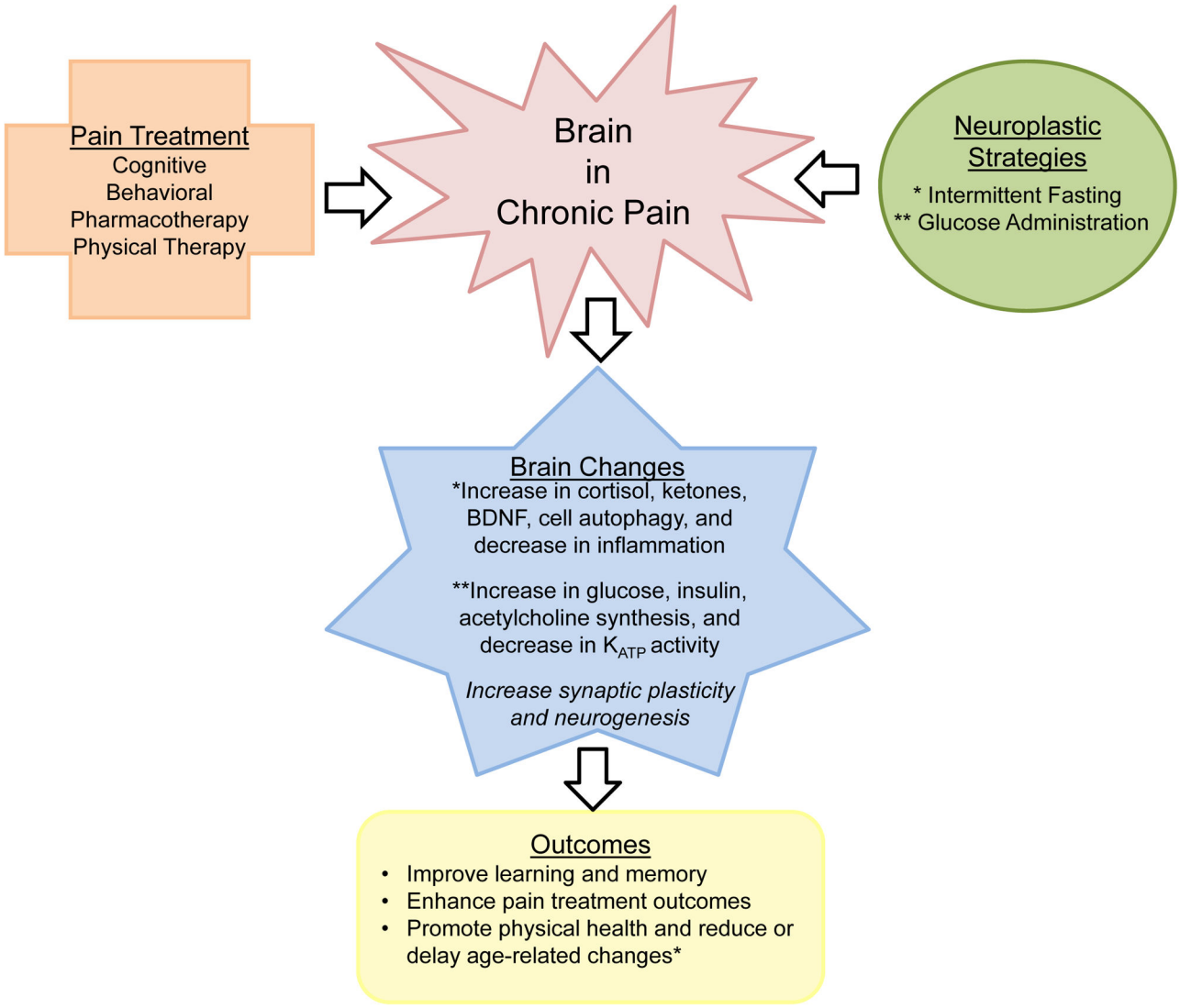

Figure 1.

Illustration of chronic pain treatment combined with neuroplastic strategies on treatment outcomes

K_{ATP}: adenosine triphosphate-sensitive potassium channel