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Nutritional Intervention in Chronic Pain: Innovative Way of Targeting Central Nervous System Sensitization?

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Summary

Introduction Few treatment programs for chronic pain nowadays take dietary pattern or adipose status into account.

Areas covered An important role of neuro-inflammation in chronic pain is now well-established, at least in part due to increased central nervous system glia activation. Based on preclinical studies, it is postulated that the interaction between nutrition and central sensitization is mediated via bidirectional gut-brain interactions. This model of diet-induced neuro-inflammation and consequent central sensitization generates a rationale for developing innovative treatments for patients with chronic pain, such as nutritional interventions and pharmacological treatments.

Methods An umbrella approach to cover the authors' expert opinion within an evidence-based viewpoint.

Expert opinion A low-saturated fat and low-added sugar dietary pattern potentially decreases oxidative stress, preventing Toll-like receptor activation and subsequent glia activation. A low-saturated fat and low-added sugar diet might also prevents afferent vagal nerve fibres sensing the pro-inflammatory mediators that come along with a high-(saturated) fat or energy dense dietary pattern, thereby preventing them to signal peripheral inflammatory status to the brain. In addition, the gut microbiota produces polyamines, which hold the capacity to excite N-methyl-D-aspartate receptors, an essential component of central nervous system sensitization. Hence, a diet reducing polyamine production by the gut microbiota requires exploration as therapeutic target for cancer-related and non-cancer chronic pain.

Article Highlights

1. Vagal afferent neurons inform the brain about dietary intake, nutritional status and peripheral inflammation, which can in turn lead to microglia activation.
2. The model of nutrition-induced neuro-inflammation and consequent central nervous system sensitization generates a rationale for developing innovative treatments for patients with chronic pain, such as nutritional interventions and pharmacological treatments.
3. A low-fat and low-added sugar diet potentially decreases oxidative stress, preventing Toll-like receptor activation and subsequent glia activation.

4. A low-saturated fat and low-sugar diet might prevents afferent vagal nerve fibres sensing the pro-inflammatory cytokines that come along with a Western diet, thereby preventing them to signal peripheral inflammatory status to the brain and induce central nervous system inflammation.
5. A diet reducing polyamine production by the gut microbiota requires exploration as therapeutic target for cancer-related and non-cancer chronic pain.
6. Preclinical studies support the idea that nutritional interventions can potentially inhibit neuro-inflammation, including glial cells activations, and consequently lead to diminished central nervous system sensitization.

Keywords: diet, pain, sensitization, gut microbiota, brain, lifestyle, microglia

1. Introduction

Pain in its acute form has been tremendously beneficial throughout evolution as it enables us to identify potential harmful stimuli and to prevent contact with them, and as it ensures we protect damaged tissue while it heals. However, once evolved into a more chronic state, its adaptive nature is superimposed by a wide range of negative sequelae that have a tremendous impact on both the individual and society. Recent reports estimated the prevalence of chronic ((post-)cancer and non-cancer) pain in the Western population as high as 30%, which is much higher than for any other chronic disease [1, 2]. Chronic pain causes the highest number of years lived with disability [3, 4] and the highest cost associated with work-related disability [5, 6]. Population-based studies also suggest that chronic pain is associated with a small decrease in life expectancy [7, 8], in part due to excess deaths from cancer and cardiovascular disease [8, 9]. Nevertheless, effective treatment options are still lacking, with 60% of those with chronic pain still experiencing pain after one year [10]. Moreover, this lack of proper pain management is thought to be a major contributing factor to the dramatic rise in overdose deaths from prescribing opioid drugs, leading to 33,000 deaths per year and an economic burden of an estimated USD 78 billion [11, 12].

Research in the neuroscience field has tremendously advanced our understanding about pain, including the role of central nervous system sensitization in the generation and amplification of (persistent) pain experiences. For the purpose of this article, we adopt the following definition of central nervous system sensitization: “an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity” [13]. Under this definition, it is possible to study central nervous system sensitization neurobiology in humans. This is not the case for other definitions such as “an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input” [14] (i.e., in vivo measurements of nociceptive neuron responses are not possible). Many patients with chronic pain lack a clear origin of nociceptive input, or the input demonstrated does not suffice to explain the experienced pain severity, related disability and other symptoms. Therefore, they are labeled as having ‘nonspecific pain’. Pain that arises from altered nociceptive function due to central nervous system sensitization has recently been labelled as ‘nociplastic pain’ by the International Association for the Study of Pain [15]. Central nervous system sensitization is a well-established feature in many patients with chronic pain

including those with chronic spinal pain [16-18], post-cancer pain [19], fibromyalgia [20], osteoarthritis [21] and pediatric pain [22].

Despite our increased understanding of the mechanisms explaining chronic pain, there is still much to learn about the development of chronic pain, including the etiological and pathogenetic mechanisms inducing and perpetuating central nervous system sensitization as a facilitator of chronicity and severe disability [23, 24]. Within this view, slowly more emphasis is given to dietary factors as a potential perpetuating factor for chronic pain [25-28]. Based on a meta-analysis of the available literature, it was concluded that an altered dietary pattern and altered specific nutrient intake may have analgesic properties for patients having chronic pain (evidence level 1a) [29]. A more recent systematic review looking at the potential link between nutritional factors and chronic musculoskeletal pain concluded that plant-based diets might have analgesic effects for patients with chronic musculoskeletal pain (evidence level 1a) [28]. Some argue that such analgesic effects of diets arises from a potential influence on central nervous system sensitization (evidence level 5) [30, 31]. Therefore, here we review the neuro-immune mechanisms potentially linking nutritional intake to central nervous system sensitization, and integrate the evidence from preclinical studies to postulate that therapeutic targeting of dietary factors might be an innovative way of treating central nervous system sensitization in patients suffering from chronic pain.

2. Methods

Given the diversity of the literature regarding neuro-immune mechanisms potentially linking nutritional intake to central nervous system sensitization, and given the large and broad area covered, a systematic or meta-analytic approach was deemed inappropriate and may even prevent reporting ideas outside the box. Therefore, this review and opinion paper applied an umbrella approach to cover the authors' expert opinion within an evidence-based viewpoint. Experts from various disciplines and various countries were asked to contribute and reflect upon neuro-immune mechanisms potentially linking nutritional intake to central nervous system sensitization and their relevance to chronic pain (management) in their writing. When evidence from human therapeutic studies is discussed, the level of evidence according the grading system from the Center of Evidence-Based Medicine [32] is provided. Level 1a refers to a systematic review of randomized clinical trials with homogeneity in the results, level 1b to an individual

randomized clinical trial with narrow confidence intervals, level 2a a systematic review of cohort studies, level 2b individual cohort studies or low quality randomized clinical trials, 2c outcomes research and ecological studies, 3a a systematic review of case-control studies, 3b an individual case-control study, 4 case series and poor quality case-control and cohort studies, 5 expert opinion, etc.) [32]. In case findings from animal studies are mentioned, it is emphasized that the results were obtained through animal research by referring to them as 'preclinical studies' or animal work, or by discussing them under a subtitle 'Animal studies'.).

3. Neuro-immune mechanisms potentially linking diet to central nervous system sensitization

Increased brain glia activation has been shown in patients with chronic pain, including those with chronic non-specific low back pain[33], fibromyalgia[34], and patients experiencing migraine attacks with aura (for at least a year)[35]. Spinal cord glia activation was found in patients having chronic lumbar radiculopathy pain [36]. An increasing number of studies suggest that aberrant glial activation might explain the establishment and/or maintenance of central nervous system sensitization, and persistent pain [33, 37-41]. Aberrant glial activity has the potential to initiate central nervous system sensitization through several mechanisms, including synthesis and release of neurotrophic factors (e.g. brain-derived neurotrophic factor) and pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), which in turn induces long-term potentiation [42] leading to enhanced neuronal synaptic efficacy [43] and, ultimately, pain sensitization [42].

As advocated in more detail elsewhere [31], an unhealthy dietary pattern characterized mainly by hyper energetic intake (e.g., high fat and/or high added sugar dietary patterns) may play a role in initiating glial activation. Poor nutritional quality (i.e., low fiber and/or hyper-energetic dietary patterns, etc.) is related to oxidative stress, tissue damage and cell necrosis not only in the gastro-intestinal tract but throughout the body, each of which are potential endogenous activators of Toll-like receptors [44]. Oxidative stress is one out of many components of inflammation. Exogenous oxidants can induce and maintain inflammation by activating Toll-like receptor 4, which in turn activates nuclear factor (NF-) kappa-β [45]. Upon activation, pattern recognition Toll-like receptors trigger the above-mentioned pro-inflammatory immune signaling events in the central nervous system, including glia activation [44,

46] (Figure 1). In addition, the established peripheral pro-inflammatory effects of an unhealthy (Western) dietary pattern [47-50], characterized by inflammatory substances in the peripheral tissues (including the gastrointestinal system), generate peripheral pro-inflammatory cytokines that can cross the blood-brain barrier and migrate into the central nervous system. High-(saturated) fat or hyper-energetic dietary patterns energy-dense diet, and the pro-inflammatory mediators (i.e. pro-inflammatory cytokines) that come along, are sensed via vagal afferent nerves in the gastrointestinal system [51, 52] that inform the brain about nutritional intake, which may in return lead to neuroinflammation [53, 54] including microglia activation [52, 55]. Indeed, vagal afferents have cytokine receptors. Binding of pro-inflammatory cytokines on those cytokine receptors activates the afferent vagal nerve fibers, subsequently triggering neuro-inflammation [53]. Mast cells located near the perivasculature within the dura on the brain side of the blood-brain barrier are strategically located: pro-inflammatory signals released from mast cells are picked up by microglia which in turn become activated [56, 57]. Conversely, neuro-inflammation can weaken not the blood-brain barrier integrity as well as the blood-spinal cord barrier [58].

Still, the above mechanisms have to be put into perspective. Nutrition is unlikely to be the sole reason why some patients develop central nervous system sensitization; it is probably a combination of interacting factors, differing from case to case. For example, animal work showed that the exposure to both sleep fragmentation and a high fat diet, compared to one of the two factors alone, leads to stronger and prolonged brain glia inflammation [59]. The authors attributed this mostly to responses associated with sleep deprivation, as they concluded that the synergistic effects of sleep fragmentation and high fat diet may be due to their independent abilities to disrupt sleep, but also that sleep disruption induces a rapid and more potent increase in microglial activation than does high-fat feeding [59]. This novel interaction between sleep and nutrition on microglial activation warrants further investigation, including studies in humans. Additionally it should be considered that also non-dietary factors such as, opioids / morphine use [60, 61], opioid withdrawal [62], long-term stress exposure and sleep problems [41] are capable of activating glia cells in the central nervous system (Figure 1).

4. Nutritional neuro-immune mechanisms: potential therapeutic targets for chronic pain?

Can we translate the neuro-immune mechanisms which link nutrition to central nervous system sensitization to potential therapeutic targets for people having persistent pain? This section explores the therapeutic potential based on animal and human studies.

Animal studies

In animals, a hypo-energetic dietary pattern (i.e., 6 weeks at 60% of the ad libitum food intake of their counterparts) inhibited neuro-inflammation, including glial cell activation, and consequently decreased central nervous system sensitization and pain behaviour [63]. Caloric restriction increased the silent information regulator 1 (SIRT1) expression, suppressed the production of reactive oxygen species and activation of nuclear factor-κβ, and decreased N-methyl-d-aspartate receptor subunits phosphorylation as well as mitogen-activated protein kinase family phosphorylation [63]. These changes were accompanied by decreased central nervous system sensitization and glia activation [63]. The same researchers reported also that such a hypo-energetic dietary pattern in non-obese rats results in antinociceptive effects on postoperative pain, possibly mediated by inhibition of inflammation [64]. Contrary to energy restriction, fasting is not indicated as a treatment for patients having chronic pain: it provides only short-term benefit and repeated use may negatively affect nutritional status and overall health [65].

Obesity negatively affects post-operative pain resolution and leads to a chronic pain state in mice [66]. The same study also found evidence supporting the idea that neuro-immune mechanisms linking nutrition to central nervous system sensitization can serve as therapeutic targets. Indeed, high fat dietary patterns prolonged post-surgical glial cell activation in the spinal cord, and altered post-surgical inflammatory markers (i.e. pro-inflammatory cytokines such as IL-1β, TNF-α and monocyte-chemoattractant protein 1) in both central and peripheral nervous systems [66]. In post-surgical mice, switching mice from the high-fat dietary pattern back to the low-fat chow, either at the time of surgery or 10 weeks later, not only lead to weight reduction and decreased inflammation, it also restored normal pain sensitivity [66]. High-fat dietary pattern increases postoperative pain particularly in male rats, and some nutritional effects did not depend on weight gain [67]: even short-term dietary manipulations that do not affect obesity may decrease postoperative pain in animals [67].

Likewise, 20 weeks of human-relevant standard American dietary pattern (i.e., high in added sugar, saturated fats, and omega-6 polyunsaturated fatty acids) prior to persistent inflammatory pain induction resulted in increased microglial activation in the spinal cord, elevated pro-inflammatory mediators and prolonged recovery from injury in rats of both sexes [68]. Conversely, a regular or anti-inflammatory dietary pattern promoted faster recovery from injury in rats [69]. In male mice, low testosterone and nutritional-induced obesity independently and cooperatively regulate neuro-inflammation in central and peripheral nervous systems, including glia activation [70].

Polyamines represent another potential therapeutic target in the area of nutritional interventions for the prevention of post-surgical pain. Polyamines are cationic organic molecules present in all living organisms, with spermidine, spermine and their precursor putrescine as the main polyamines in mammalian cells [71]. Human gut bacteria synthesize and transport polyamines [71], and polyamine levels increase with inflammation [72]. Polyamines are thought to be involved in the regulation of numerous metabolic and electrophysiological processes in the nervous system, including scavenging of reactive oxygen species, and alteration of polyamine metabolism has been identified in neurodegenerative disease and several types of cancer, resulting in increased interest of exogenous administration of natural polyamines as innovative treatment [71]. Animal studies support the idea that a polyamine-deficient dietary pattern has analgesic effects on inflammatory pain [73] and reduces pain hypersensitivity [74]. Excitation of N-methyl-D-aspartate (NMDA) receptors is an essential component of central nervous system sensitization, with polyamines holding the capacity to modulate them [72]. Polyamine-deficient dietary pattern is thought to inhibit tyrosine phosphorylation of the NMDA receptors [72], thereby potentially decreasing the sensitivity of the (central) nervous system.

Together, these preclinical studies provide proof of concept for human studies exploring the benefits of nutritional interventions in preventing post-surgical pain in non-cancer (e.g. spinal surgery, joint replacement surgery, transplantation) and cancer populations where excessive post-surgical pain is often seen and represents a major side effect and long-term sequel.

The metabolic state of ketosis induced by a ketogenic diet has been investigated in animals and shows potential as a nutritional therapy for pain [75]. Increased ketone body concentration, coupled with a reduction of blood glucose, holds the potential to influence several pathways, including decreased oxidative stress, and reduced neuronal excitability. This neuronal inhibition might be due to the ketogenic diet effect on gamma-aminobuteric acids (GABA), a neurotransmitter most often exerting inhibitory action in the central nervous system [76]. In rat studies ketogenic diets have been found to produce significant hypoalgesia to thermal pain [77].

In addition to inspiring the study of nutritional interventions for patients having chronic pain, our increased understanding of the potential role of inadequate nutrition, neuro-inflammation and central nervous system sensitization in patients having chronic pain may also lead towards developing new pharmacological treatments. Based on the possible role of the gut microbiota in mediating nutritional-induced neuro-inflammation and subsequent central nervous system sensitization, the gut microbiota might represent another innovative therapeutic target [78], also potentially influencing polyamine production by gut microbes. In patients with primary sclerosing cholangitis and/or inflammatory bowel disease, an increased prevalence of Bacteroides 2 enterotype was observed across the pathologies studied, with microbial loads inversely associated with intestinal and systemic inflammation markers [79], supporting the link between gut microbiota and peripheral inflammation. Still, studies exploring the possible role of microbiota in triggering poor nutritional-induced neuro-inflammation and subsequent central nervous system sensitization are needed before they can be considered as therapeutic targets for patients suffering from chronic pain.

Another potential therapeutic way of targeting neuro-inflammation in chronic pain relates to the mast-cell glia axis in neuro-inflammation. Activated mast cells may contribute to glial activation through its release of an array of mediators after degranulation, including pro-inflammatory cytokines (IL-1β, TNF-α) and nerve growth factor [80]. Mast cells and microglia interact in a bidirectional fashion, including through Toll-like receptors isoforms-2 and -4, mast cell tryptase and proteinase-activated receptor 2 on microglia [80]. The naturally occurring fatty acid *N*-palmitoylethanolamine (or palmitoylethanolamide) is an endogenous molecule abundant in the mammalian brain with established anti-inflammatory and analgesic properties, potentially through inhibiting mast cell activation [80]. This way, they hold potential as innovate therapeutic target for chronic postsurgical and nonsurgical pain.

Resolvins are a final potential nutritional therapeutic route of targeting neuro-inflammation in chronic pain inspired by animal studies. In addition to pro-and anti-inflammatory mediators, resolvins represent a group of mediators involved in the active process of resolution of inflammation. Resolvins from the resolving D-series are derived from omega-3 polyunsaturated fatty acids, and hold more powerful analgesic properties than the omega-3 polyunsaturated fatty acids themselves [81]. Their analgesic properties are believed to be mediated in part due to glial modulation [82]. In male, but not in female mice, resolvin D5 inhibited chemotherapy-induced neuropathic and inflammatory pain [81]. Is it possible to 'replace' intrathecal injection of resolvins by a nutritional intervention that increases the availability of resolvins in patients having chronic pain?

Human studies

Based on a meta-analysis of the available literature, it was concluded that an altered dietary pattern and altered specific nutrient intake may have analgesic properties for patients having chronic pain(evidence level 1a)[65]. Some argue that such analgesic effects of diets arises from a potential influence on central nervous system sensitization (evidence level 5) [30, 31]. This idea is supported by a study demonstrating reduced self-reported neuropathic pain intensity scores (large effect size) after a 12-week anti-inflammatory dietary pattern in neuropathic pain patients (evidence level 4) [83]. Still, the study was small (n=20) and has some methodological limitations: it applied a parallel group design and the two groups showed baseline differences. Also, among patients with fibromyalgia, a condition characterized by central nervous system sensitization [84], a pro-inflammatory diet was associated with psychophysiological tests of pain hypersensitivity (evidence level 4) [85].

Human studies regarding possible pain-relieving effects of nutritional interventions are mostly available from the osteoarthritis-field. For instance, results from a randomized controlled pilot study suggest a 12 weeks low-carbohydrate dietary intervention, but not a low-fat dietary intervention, could provide relief from pain, reduce oxidative stress, improve quality of life, and be an opioid alternative in patients with knee osteoarthritis (evidence level 2b) [86]. Research in the osteoarthritis field also indicates a superiority of multimodal over single-mode interventions. Among overweight and obese adults with knee osteoarthritis, a combined intervention of nutritional and exercise therapy was superior over exercise therapy alone in weight loss and reduced interleukin (IL)-6 levels

(evidence level 1b) [87]. Such an added value of diet over exercise therapy is important as the anti-inflammatory effects of exercise therapy are well established [88-93], potentially masking anti-inflammatory effects of dietary interventions in combined approaches. Also, the change in inflammatory factors after the combined nutritional and exercise intervention, rather than the change in body mass index (BMI), mediated the effect on pain and function in overweight and obese patients with knee osteoarthritis [94]. All trials in overweight and obese adults with knee osteoarthritis combined show that moderate pain relief and improved physical function is achievable with a combination of nutritional and exercise therapy, whilst treatment effects on inflammatory biomarkers are questionable as they have not been shown consistently across studies (evidence level 1a) [95]. Moreover, nutritional and exercise therapy added to usual care is cost-effective for overweight and obese patients with knee osteoarthritis and should be implemented in clinical practice (evidence level 1a) [96]. Still, it may be purely the beneficial biomechanical effects and improved body composition (including decreased fat mass) of weight loss that explains improvements in pain following a combined dietary and exercise intervention, rather than nutritional effects on inflammation.

An innovative study found that following a nonsurgical weight loss program, including changes in nutritional behavior and exercise, obese patients with chronic low back pain (n=46) not only lost body weight but also experienced less pain and disability (evidence level 4) [97]. After 14 weeks, a remarkable clinically important mean improvement in low back pain (48% pain reduction) was found [97]. Although compelling, the study was uncontrolled (pre-experimental design), precluding causal interpretation of the study findings. A telephone-based behavioral lifestyle intervention was unable to alter lifestyle behaviors, i.e., dietary pattern, physical activity and body weight, had a low compliance rate (29%), and consequently did not reduce pain intensity in overweight or obese patients with low back pain (evidence level 1b) [98, 99]. Therefore, a face-to-face intervention could be preferred over long-distance treatment to obtain the lifestyle changes required for improving pain in overweight patients having chronic pain. A recent systematic review found effect sizes for eHealth interventions combined with remote counseling (e.g. videoconferencing and e-mail support) which were only slightly lower compared to eHealth interventions combined with face-to-face interventions, but with a considerable lower economic impact for the former (evidence level 1a) [100]. This was confirmed by a study revealing that conventional weight loss programs could be replaced in part by a mobile application without compromising on the effectiveness (evidence level 1b)

[101]. Thus, the optimal format for behavioral lifestyle interventions, considering both the effectiveness and the economic impact, seems to be a combination of a mobile application and behavioral support through counseling (evidence level 1a) [100, 101].

The established positive association between BMI and persistent pain after breast cancer surgery (evidence level 3a) [102] fuels the importance of exploring the above-mentioned animal findings regarding possible effects of energy dense dietary patterns on post-surgery neuroinflammation and pain severity in selected patient populations. Unfortunately, early findings point towards mixed effects of pre-surgical energy restriction on tumor biology in primary breast cancer (evidence level 2b) [103], rendering ethical concerns to explore this idea to prevent post-surgical pain in humans having primary breast cancer. Therefore, nutritional interventions in cancer populations may be better timed after surgical resection (evidence level 5) [103], but still hold great potential for preventing post-surgical pain in non-cancer patients at risk of developing post-surgical pain (e.g., spinal surgery, joint replacement surgery, transplantation).

For instance, the potentially sensitizing effects of polyamines, together with the above-mentioned animal study showing analgesic effects of a polyamine-deficient dietary pattern [73], provided the rationale to undertake a randomized, multicenter phase II clinical trial comparing a perioperative (7 days before until 5 days after surgery) total polyamine deficient versus partial polyamine dietary pattern in patients undergoing surgery for chronic low back pain [72]. Proof of concept was provided for the short-term pain-relieving effects of the polyamine deficient condition in patients undergoing spinal surgery, but without long-term effects (evidence level 2b) [72]. Still, the study was supported by a company manufacturing polyamines dietary supplements. Therefore, these interesting findings require more and independent studies in this area. Although available human studies suggest that a polyamine-deficient diet is well-tolerated [72, 104], studies examining whether is causes adverse effects in patients having chronic pain are needed. A trial aimed at evaluating the efficacy and feasibility of a polyamine-deficient diet compared to a normal polyamine containing diet to prevent peripheral neuropathy in patients undergoing chemotherapy for advanced colorectal cancer is ongoing [105].

Likewise, the interesting animal findings regarding potential analgesic and desensitizing effects of ketogenic diet [77, 106] require extrapolation in humans having chronic pain. Currently, clinical trials exploring the effects of ketogenic diet in patients having chronic pain are essentially lacking; human studies of ketogenic diet in patients having chronic pain are limited to small scale observational (uncontrolled) studies (e.g., [107, 108]; evidence level 4).

Last, food additives hold the potential to impact the gut microbiota in mice [109], immune cells [110], and might contribute to neuronal excitability and neuroinflammation evidence level 2b) [111] in patients with chronic pain. The neurotransmitter glutamate is a common dietary additive known to overexcite neurons, has been linked to central nervous system sensitization [112], and its removal from the diet has been explored in a study of patients with fibromyalgia who also had irritable bowel syndrome (evidence level 2b) [111]. Fifty-seven patients were placed on a 4-week diet that eliminated the dietary additive excitotoxins including monosodium glutamate and aspartame. Thirty-seven patients completed the diet and 84% of those reported that >30% of their symptoms resolved, thus making them eligible to proceed to a glutamate challenge [111]. These patients were then randomized to a 2-week double- blind placebo-controlled crossover challenge with monosodium or placebo for 3 consecutive days each week. The monosodium challenge, as compared to placebo, resulted in a significant return of symptoms, a worsening of fibromyalgia severity, and decreased quality of life in patients with fibromyalgia who also had irritable bowel syndrome and initially responded well to a diet eliminating additive excitotoxins [111]. This study suggests a possible role for food additives such as glutamate in explaining symptoms of central nervous system sensitization in patients with fibromyalgia and comorbid irritable bowel syndrome.

5. Conclusion

An important role of neuro-inflammation in chronic pain is now well-established [36, 39, 113], at least in part due to increased central nervous system glia activation as observed in patients with chronic non-specific low back pain [33], chronic lumbar radiculopathy pain [36], patients experiencing migraine attacks with aura (for at least a year) [35] and fibromyalgia [34]. Such neuroinflammation can explain the increased excitability of the central nervous system [41]. Based on preclinical studies, it is postulated that the interaction between nutrition and central nervous

system sensitization is mediated via bidirectional gut-brain interactions. More specifically, vagal afferent neurons inform the brain about dietary intake, nutritional status and peripheral inflammation (whether or not diet-induced) [51], which can in turn - depending on the dietary pattern - lead to microglia activation [52, 55].

This model of nutrition-induced neuro-inflammation and consequent central nervous system sensitization generates a rationale for developing innovative treatments for patients with chronic pain, such as nutritional interventions and pharmacological treatments. Moreover, several potential therapeutic targets can be defined based on this framework of neuro-immune mechanisms linking nutrition to central nervous system sensitization. These include, but are certainly not limited to, oxidative stress (i.e., free radicals and antioxidants), pattern recognition Toll-like receptors, afferent vagal nerve fibers and the gut microbiota (Table 1). A low-fat and low-added sugar diet potentially decreases oxidative stress, preventing Toll-like receptor activation and subsequent glia activation (figure 2). Likewise, a low-saturated fat and low sugar diet might prevent afferent vagal nerve fibres sensing the pro-inflammatory mediators that come along with a Western diet, thereby preventing them to signal peripheral inflammatory status to the brain and induce central nervous system inflammation.

In addition, a high-protein diet increases fermentation of proteins by colonic microbiota, resulting in the production of protein fermentation end-products such as polyamines [114]. Polyamines (mainly spermine, spermidine, putrescine and cadaverine) regulate protein translation, gene transcription and metabolic functions, but their catabolism may also impair metabolic functions through production of toxic by-products [114]. In line with this, polyamines hold the capacity to excite NMDA receptors, an essential component of central nervous system sensitization. Hence, a diet reducing polyamine production by the gut microbiota (i.e. reducing polyamine uptake by selecting low polyamine-containing food and reducing bacterial gut production of polyamines [104]) requires exploration as therapeutic target for cancer-related and non-cancer chronic pain.

Preclinical studies support the idea that nutritional interventions can potentially inhibit neuro-inflammation, including glial cells activations, and consequently lead to diminished central nervous system sensitization [63, 64, 66, 69, 73,

74]. Human studies regarding possible pain-relieving effects of nutritional interventions are mostly available from the osteoarthritis-field, and show that altered dietary pattern and altered specific nutrient intake results in significant pain relief in patients having chronic pain (evidence level 1a) [65]. Studies exploring the outlined mechanisms in patients having chronic pain are essentially lacking and are therefore an important research priority. In addition, human studies have not provided a consistent view of the effects of nutritional interventions on inflammatory cytokines. Therefore, one should be cautious when findings from preclinical studies are extrapolated to humans.

6. Expert opinion

In the absence of specific dietary advice, patients having chronic pain may have poor dietary intake. For instance, daily diet in patients with rheumatoid arthritis was found to be significantly deficient in calories, proteins, calcium and potassium (evidence level 3b) [115], underscoring the need for adding dietary guidance to the multimodal treatment of chronic pain. Understanding central nervous system sensitization and its role in relation to chronic pain has implications for clinicians integrating dietary interventions into a multimodal treatment for chronic pain. The awareness is growing that there is a large implementation potential, as nowadays not so many clinicians integrate dietary interventions into the multimodal management of chronic pain. We hope the present paper will contribute to increasing awareness and inform clinicians about the therapeutic potential of dietary interventions for managing chronic pain and central nervous system sensitization.

However, clinicians should not interpret the presence of central nervous system sensitization the wrong way: central nervous system sensitization is not fixed, therapeutic targeting allows for it to improve. For instance, we previously showed that multimodal management of chronic pain taking central nervous system sensitization into account (i.e. pain neuroscience education and cognition-targeted exercise therapy) was able to ameliorate sensitization substantially (medium to large effect sizes; evidence level 1b) [116]. However, similar to how exercise therapy and graded activity are applied to patients having chronic pain and central nervous system sensitization, clinicians providing dietary interventions should not rely on short-term changes in pain (severity). Contrary to acute pain where pain has a messenger function to alert us of potential danger, central nervous system sensitization implies

that pain is produced without actual or threatening tissue damage. As a consequence, pain due to central sensitization is no longer a reliable messenger. Hence, when patients having chronic pain and central nervous system sensitization apply a new diet, they should not adapt it to short-term variances in pain (e.g. a patient that eliminates certain nutritional elements from the diet in response to acute pain flares). Moreover, adapting diets to short-term variances in pain will reward the brain in producing pain, and consequently will make the situation worse. Possible benefits of dietary changes should be evaluated based on long-term improvements rather than immediate changes in pain (severity). Focusing on such long-term improvements implies taking central nervous system sensitization into account.

Given the body of evidence from preclinical studies supporting a close interplay between nutrition and central nervous system sensitization mediated via bidirectional gut-brain interactions, it seems appropriate to explore these interactions in human studies, especially in patients having chronic pain. In view of the available evidence from treatment studies in both animal models of chronic pain and patients having chronic pain, a combined nutritional and general exercise intervention is advocated for patients having overweight or obesity and chronic pain. For instance, in addition to nutritional intake, physical activity is likely to be another lifestyle factor that influences the diversity of gut microbiota (evidence level 2b) [117]. Both animal and human studies support the idea that exercise improves diversity of gut microbiota (figure 2), but the evidence in humans is weak and requires further examination, including dose-response studies [117].

Alternatively, to targeting weight reduction per se, an anti-inflammatory dietary pattern might address central nervous system sensitization and underlying neuro-inflammation more directly [83]. Such anti-inflammatory dietary pattern may include providing food items containing high anti-inflammatory components, such as polyphenols (i.e. antioxidants), high amounts of fruits (e.g. grapes, apple, pear, cherries, berries, etc.), vegetables (e.g. artichoke, kale, red cabbage, beans, spinach, pecans, etc.) and cereals [118]. In other words, the prescribed anti-inflammatory dietary pattern should focus mainly on foods with a high ferric reducing antioxidant power [118, 119]. Past research informed us that daily incorporation of some of these items, such as blueberries, may reduce inflammation and pain

in patients having chronic pain (evidence level 1b) [120]. Principles of motivational interviewing can be used to co-develop the anti-inflammatory dietary pattern [121].

Details of authors contributions

All authors provided writing, literature review, acquisition of data, analysis and interpretation of literature data, and editing/critical review of the paper, including revising it critically for important intellectual content prior to submission. JN provided concept, idea and writing up of the first draft of the paper. All authors gave final approval of the version to be submitted, and agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of interest

The authors report no conflict of interest.

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Figures

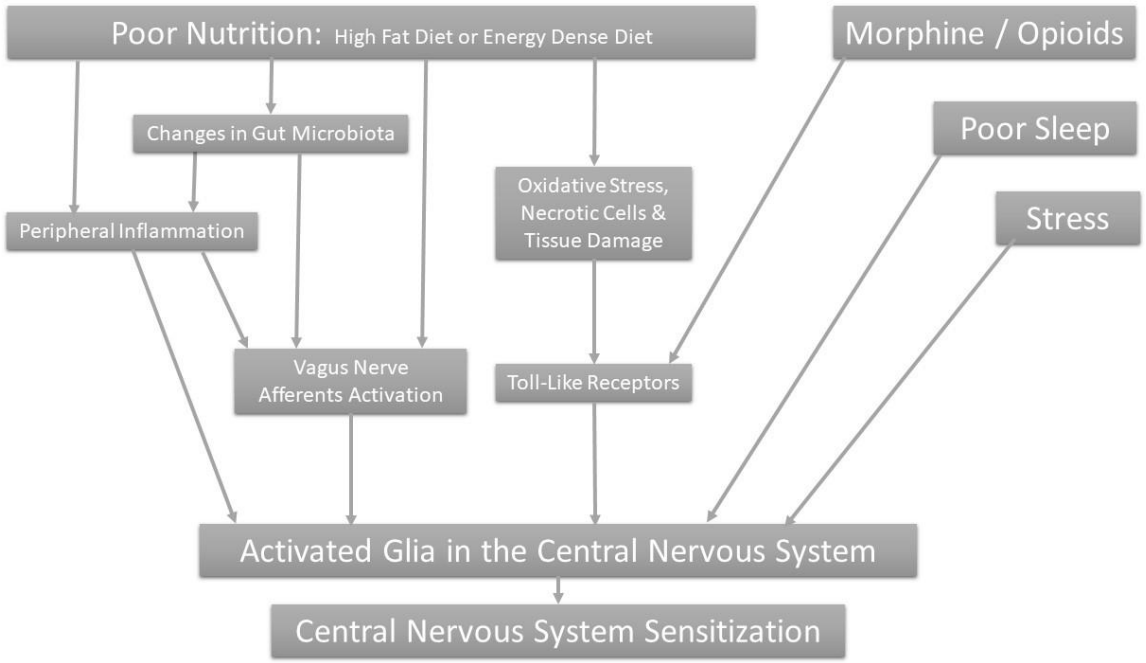

Figure 1: Neuro-immune mechanisms potentially linking dietary pattern, opioids, stress and sleep problems to central nervous system sensitization (modified from [31]).

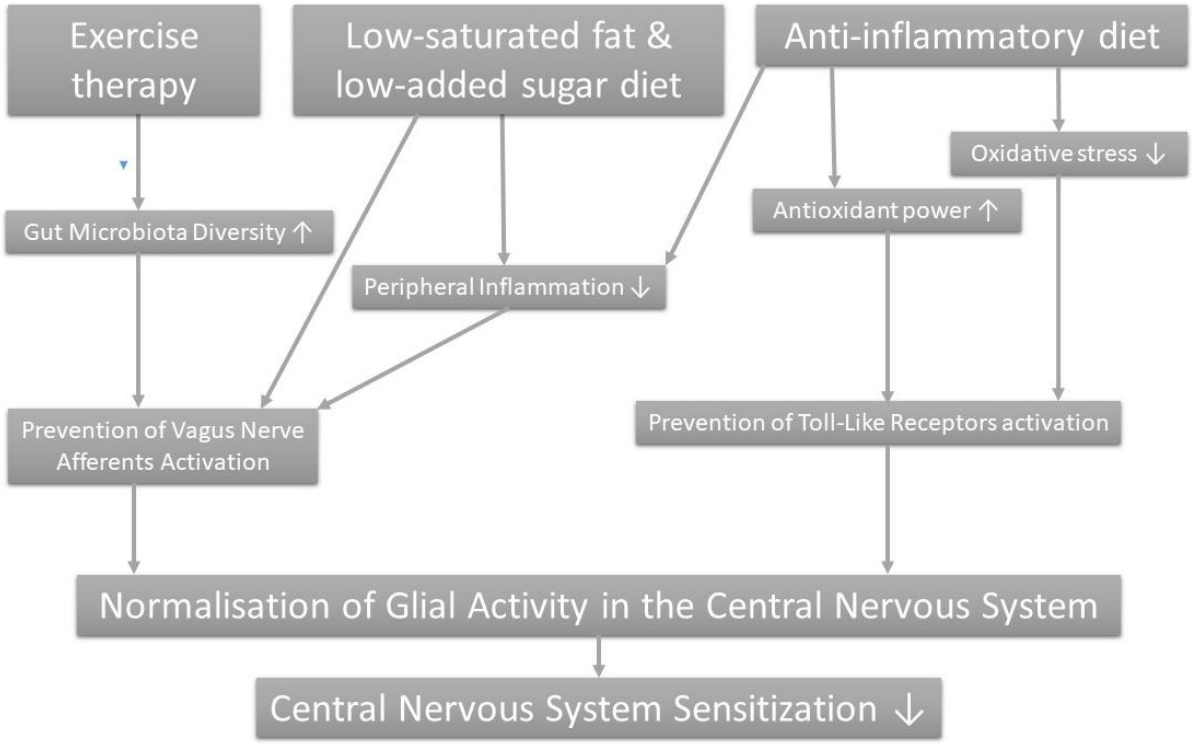

Figure 2: Proposed mechanisms explaining how a healthier diet can lead to less neuro-inflammation (and less central nervous system sensitization) in patients having chronic pain.

Tables

Table 1: Potential therapeutic targets within the framework of neuro-immune mechanisms linking diet to central nervous system sensitization, based on preclinical studies.

	Potential therapeutic target	Targeted mechanism
1.	Oxidative stress, either by decreasing or neutralizing free radicals, or by boosting antioxidants	Released in response to high fat or high sugar diet, potential endogenous activators of Toll-like receptors.
2.	Pattern recognition Toll-like receptors	Their activation trigger pro-inflammatory central nervous system immune signaling events, leading to (more) central sensitization.
3.	Afferent vagal nerve fibers	Sense high-(saturated) fat or energy dense dietary pattern, and the pro-inflammatory mediators that come along, in the gastrointestinal system. This way, they inform the brain and induce central nervous system inflammation.
4.	Microglia	Key factor in neuro-inflammation and related central nervous system sensitization.
5.	Gut microbiota	Possible role in triggering poor diet-induced neuro-inflammation and subsequent central nervous system sensitization.
6.	Polyamines	Hold the capacity to modulate (i.e., excite) N-methyl-D-aspartate (NMDA) receptors, which is an essential component of central nervous system sensitization.
7.	Neurotransmitters	Modulation of neuronal excitability via gamma-amino-butyric acid and glutamate production.

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Reference annotations (*=of importance, **= of considerable importance)

Reference number 33**: First study showing brain glia activation in patients having nonspecific chronic pain.

Reference number 51*: Important work revealing gut-brain axis communication that is key for the main ideas presented here.

Reference number 52*: Important work revealing gut-brain axis communication that is key for the main ideas presented here.

Reference number 53**: Hallmark paper in the field of psychoneuroimmunology.

Reference number 95*: Important meta-analysis summarizing the available clinical studies regarding the added value of dietary interventions in overweight or obese patients with osteoarthritis.

Reference number 103*: Important study that provides key findings for guiding future work in this area.