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Topical review

Food, pain, and drugs: Does it matter what pain patients eat?

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1. Introduction

In 2003, the World Health Organization published a report on the global change in diet resulting from industrialization, urbanization, and market globalization, and the impact on the development of chronic disease [12]. The adverse dietary changes are characterized by a high-energy density diet with greater intake of saturated fats and sugars, reduced complex carbohydrates, dietary fibre, and reduced fruit and vegetable intakes. Modern dietary patterns are considered to be *risk behaviours*, and the World Health Organization identifies nutrition as a "*major modifiable determinant of chronic disease.*"

The importance of nutrition in promoting health and preventing disease is well established. The central nervous system has specific nutritional requirements. Essential fatty acids such as eicosapentaenoic, arachidonic acids, and tryptophan (the precursor of serotonin) are not synthesized by mammals, but derived from foodstuffs. Micronutrients are important for central nervous system function; vitamin B12 and folate deficiencies result in painful peripheral neuropathy, while vitamin D deficiency causes musculoskeletal pain. Scurvy, which causes bone pain and myalgia, is still present in developed countries [22,38]. Malnutrition is a growing problem in industrialized countries and appears to be related to the abundance and availability of the wrong kind of food [35]. Other contributing factors are eating disorders, food allergies, and fad diets.

Nutritional strategies may be useful for improving pain management. Such strategies include optimizing the diet to ensure adequate intake of vitamins and essential amino acids, increasing intake of foodstuffs that reduce pain, and restricting foodstuffs that may facilitate pain or reduce the effectiveness of oral analgesics.

2. Getting the right balance: the omega-3/omega-6 ratio

During the last half of the 20th century, there has been a considerable change in the quantity and quality of fat consumed, with increased use of vegetable oils in exchange for dairy fat to reduce the intake of saturated fat. Many vegetable oils, for example, soya oil, have a high content of omega-6 polyunsaturated fatty acids (PUFAs). At the same time, the consumption of fish and marine-based omega-3 PUFAs has decreased, and animal feed is now largely based on corn, increasing the omega-6-to-omega-3 ratio in animal products. The sum effect of these changes is a considerably higher ratio of omega-6/omega-3 in food globally – so that the presumed "ideal" ratio of 1:1 is now 10-15:1 [6,32]. The recommended intake of long-chain omega-3 PUFAs is 500 mg per day, but the actual intake in Western countries is much lower [19].

Consumption of omega-6 PUFAs such as arachidonic acid is important for the body's defence against infections. Metabolism of arachidonic acid has a *proinflammatory* effect by increasing production of leukotrienes and prostaglandins. However, too high an intake may contribute to the chronic inflammation that characterizes lifestyle diseases such as obesity, type 2 diabetes, and cardiovascular illness. The omega-3 PUFAs docosahexaenoic acid and eicosapentaenoic acid are competitive substrates for conversion of arachidonic acid. Hence, dietary omega-3 PUFAs compete with omega-6 PUFAs for substrate and reduce proinflammatory responses by decreasing overall production of prostaglandin E_2 and leukotriene B_4, and by increasing production of prostacyclin (PGI_3) and leukotriene B_5 [8,31].

The dietary *omega-3/omega-6 ratio* may have significance for inflammatory pain. Omega-6 PUFAS have been implicated in osteoarthritis [26]. Recent preclinical findings suggest specific roles of resolvins derived from omega-3 PUFAs in regulating transient receptor potential subtype channels [24]. A systematic review that included 17 randomized controlled trials concluded that omega-3 supplementation reduces patient-reported joint-pain intensity, minutes of morning stiffness, number of painful joints, and nonsteroidal antiinflammatory drug consumption in patients with rheumatoid arthritis or joint pain secondary to inflammatory bowel disease [15].

3. The *N*-methyl-D-aspartate receptor: dietary polyamines and magnesium

Clinical pain is now known to be not just a reflection of sustained noxious input, but also the expression of neural plasticity.

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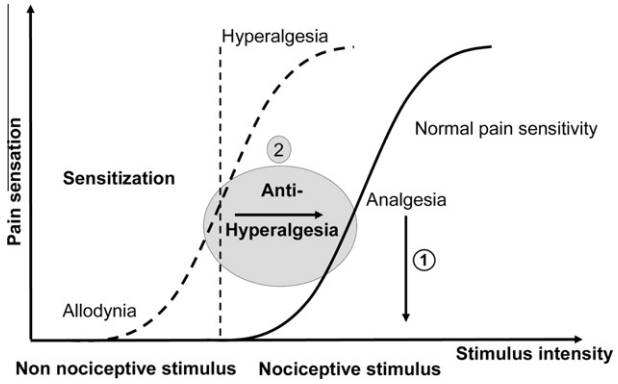

Fig. 1. Relationships between nociceptive stimulus intensity and pain sensation level illustrating the concept of an "anti-hyperalgesia strategy" (2); which differs from an "analgesia strategy" (1).

These neurobiological changes lead to both peripheral and central sensitization – increasing the "gain" [39] of transmitted pain signals that clinically elicit hyperalgesia/allodynia (Fig. 1). This process facilitates the development of chronic pain. The reduction or prevention of central sensitization offers new possibilities for innovative therapeutic strategies, such as nutritional therapies, which could be complementary to classical analgesic use. Interestingly, it is thought that these sensitization processes are supported by neural systems that are different from the classical pain pathways. Numerous studies indicate that overactivation of excitatory glutamate/*N*-methyl-D-aspartate receptor (NMDA-R) systems, particularly the NR2B subtype [9], plays a critical role in the activity-dependent central sensitization process [39]. However, the use of NMDA-R antagonists is limited due to unacceptable adverse effects, although newer drugs that are selective for the NR_2B receptor subunit have demonstrated a better therapeutic profile in animal models. To avoid the deleterious effects associated with NMDA-R antagonist use, an alternative strategy is to target allosteric sites rather than orthosteric sites. One way of doing this is to reduce dietary polyamine intake.

Polyamines (spermine, spermidine, and putrescine) are organic polycations at physiological pH, which positively modulate NMDA-R function by shielding the NR1-located H^+-sensor from protons, thus attenuating the inhibition of the NR1-NR2B channel functioning by protons [21]. By positively modulating the NR1 polyamine sites, polyamines facilitate pain sensitization. Since polyamines mainly originate from dietary intake and gut bacterial metabolism [4,10], a polyamine-deficient diet (PD diet) could be a nutritional strategy to counteract the deleterious effect of upregulated NMDA activity and subsequent pain sensitization.

Preclinical studies in the rat have shown that a PD diet strongly reduces long-lasting hyperalgesia induced by tissue injury (inflammation or surgical incision) [27]. In contrast, an enriched polyamine diet induces an exaggerated hyperalgesia, suggesting that polyamine level plays a critical role in pain hypersensitivity. A PD diet also prevents paradoxical hyperalgesia (pain vulnerability) induced by non-nociceptive environmental stress after surgery [27]. From a mechanistic viewpoint, it has been established that a PD diet prevents the enhancement of tyrosine phosphorylation of the spinal NR2B subunit-containing NMDA receptors associated with tissue injury [27]. Moreover, a PD diet reverses the sustained pain hypersensitivity associated with monoarthritis or neuropathy and restores the analgesic effect of morphine without inducing the adverse effects commonly induced by NMDA receptor antagonists [27] (see Fig. 2).

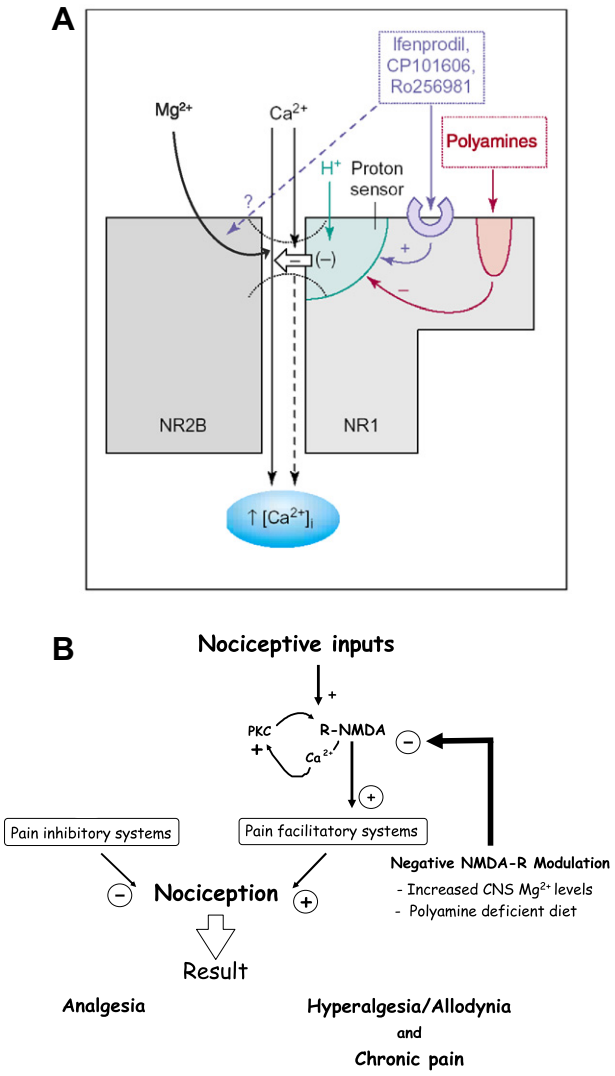

Fig. 2. Polyamine and Mg2+ interactions at the *N*-methyl-D-aspartate (NMDA) receptor level leading to hyperalgesia. (A) Schematic representation of the NMDA receptor complex. (B) Pain sensation level results from an equilibrium between inhibitory and facilitatory pain systems. Polyamines and Mg2+ act, respectively, as positive and negative modulators in pain facilitatory systems. Decreasing intake of polyamines and maintaining adequate Mg2+ levels at the NMDA receptor level act to oppose overactivation of NMDA receptors leading to hyperalgesia.

Although these results are currently limited to preclinical studies, we can speculate that restricting polyamine intake may facilitate clinical management of pain by reducing pain hypersensitivity and by restoring the effectiveness of classic analgesics. A recent report in hormone refractory prostate cancer patients indicated that a sustained reduced consumption of polyamine-containing foodstuffs for several months was well tolerated [11].

Magnesium is a physiological NMDA-R blocker, and it has been proposed that magnesium deficiency may facilitate NMDA-R activation and long-term sensitization of nociceptive pathways [5]. A recent randomized, placebo-controlled clinical trial in patients with neuropathic pain found that oral magnesium reduced the frequency of pain paroxysms, although there was no difference in pain relief between groups after 1 month of treatment [25]. Could foods naturally high in magnesium, such as chocolate, green leafy vegetables, almonds, avocados, pumpkin, and banana [36] be potential adjuvants to improve the effect of NMDA-R antagonists

or PD diet by reducing NMDA-R overactivation, especially in patients with hypomagnesaemia?

4. Antihyperalgesic effects of dietary constituents

There are over 5000 identified flavonoid compounds in plants that are generally classified into flavones (eg, quercetin), isoflavonoids (eg, genistein), neoflavonoids (eg, nivetin), anthocyanidins (eg, cyanidin), and flavanols (eg, catechin). Various foods or food extracts containing flavonoid compounds have been suggested to have antioxidant and antiinflammatory properties that can have antihyperalgesic effects. Multiple mechanisms of action at peripheral and central targets have been suggested, such as inhibition of nuclear factor-κB, mitogen-activated protein kinase, and cyclooxygenase signalling, or inhibition of lipid peroxidation, just to name a few (for review, see [33]). However, the direct in vivo efficacy of flavonoids has been questioned due to their poor absorption and fast metabolism [18]. Nevertheless, several animal and clinical studies in vivo reported beneficial effects of flavonoid supplementation in outcome measures related to pain or range of motion. For example, there are animal studies which indicate that tart cherries (rich in anthocyanins) or tea compounds (like quercetin) can dose- dependently reduce hyperalgesia associated with inflammation or streptozotocin-induced diabetic neuropathy, respectively [1,34].

Numerous publications suggest that soy has antihyperalgesic effects because of antiinflammatory and antioxidant effects of flavonoid compounds it contains. A number of animal studies first demonstrated that prophylactic consumption of soy reduces hyperalgesia after nerve injury, bone cancer, or inflammation (for example [7,30,40]). More recently, Valsecchi et al. reported that genistein (isoflavone present in soy) dose-dependently attenuates mechanical and heat hyperalgesia after chronic constriction injury or streptozotocin-induced diabetic neuropathy [37] by their preferential binding affinity to oestrogen receptor β, and by reducing reactive oxygen species (eg, hydroperoxide).

Whereas flavonoid compounds will never become a "cure all" for treating pain, the existing body of literature suggests that ingestion of flavonoids may be beneficial in reducing some types of persistent pain. Flavonoid consumption may also improve the therapeutic profile of currently available antiinflammatory medications by reducing the dose necessary to achieve pain relief. Well-designed clinical trials are needed to understand the benefits and limitations of flavonoids in improving pain and related outcome measures.

Other dietary constituents with promising evidence for antihyperalgesic effects are antioxidants such as alpha-lipoic acid and vitamin E, as recently reviewed by Lee and Raja [16]. Alpha-lipoic acid is present in green leafy vegetables such as spinach and broccoli, and in yeast. A recent systematic review found that alpha-lipoic acid administered as an oral or intravenous supplement over a 3-week period provided a significant and clinically relevant decrease of pain in patients with diabetic polyneuropathy [20].

5. Pharmacokinetic food-drug interactions

Food and medication are often taken together. Food can interfere with the pharmacokinetics of drugs through different mechanisms. Fatty food decreases the motility of the gastrointestinal tract and can decrease drug absorption. Minerals bind several drugs in the gastrointestinal tract, reducing their absorption. Both Fe and Zn form insoluble complexes with several antibiotics, for example, ciprofloxacin [17].

Fruit juice consumption has increased, especially in developed countries. Fruit juices can interfere with the metabolism and excretion of several drugs through different mechanisms. CYP3A4/5 contributes to the metabolism of an estimated 50% of all drugs [13]. Grapefruit juice inhibits CYP3A4/5-mediated first-pass metabolism and can increase the oral bioavailability of drugs 3-fold [3].

Fruit juices can also interfere with drug metabolism by inhibiting drug transporters. Grapefruit juice is a relatively potent inhibitor of P-glycoprotein, an efflux transporter [23].

The major flavonoid in grapefruit, naringin, has been shown to inhibit P-glycoprotein activity by 50% in vitro. On the other hand, orange juice and its major flavonoid hesperidin have been shown to be potent in vitro inhibitors of the uptake transporter OATP1A2 at relatively low concentrations [2]. Also, other juices (apple, pomelo, turmeric, and ginger) have been shown to interfere with drug metabolism [2,14].

Caffeine is increasingly consumed, either as coffee, cola, or other caffeinated beverages [28]. Caffeine is an adenosine A1 and A2 receptor blocker. Chronic caffeine consumption is related to withdrawal headache and sleep disturbance. Low doses of caffeine have been shown in animal studies to inhibit antinociception by amitriptyline, venlafaxine, carbamazepine, oxcarbazepine [28], and acetaminophen [29].

6. Conclusions

Adequate nutrition is a basic premise for good health, including pain relief. We suggest that the evaluation of diet should be a routine part of the medical work-up for chronic pain, on a par with other lifestyle factors such as exercise and sleep. Future research should focus on pain patients' dietary habits, including intake of polyamines, omega-3 and omega-6 PUFAs, vitamin D, and caffeine; and the effects of diet on analgesic treatment. Despite an increasing number of preclinical trials demonstrating a role for nutritional factors in pain, epidemiological and clinical trials are lacking. Well-designed trials are needed to investigate the antihyperalgesic effects of PD diet, $Mg2^{+}$, flavonoids, and antioxidants, and to further explore the potential of nutritional therapy in pain patients.

Conflict of interest statement

The University of Victor Ségalen Bordeaux 2 and University of Rennes 1 have a patent (G. Simonnet and J.P. Moulinoux are co-inventors) on a human form of polyamine-deficient diet adapted and modified from rat chow. A patent licensing arrangement has been established between University of Bordeaux 2, University Rennes 1, and Nutrialys Medical Nutrition SA, France (G. Simonnet and J.P. Moulinoux are founder members and shareholders in Nutrialys Medical Nutrition SA) concerning this nutritional therapy. Nutrialys has not given financial support to any experimental studies developed by G. Simonnet et al.

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