Abstract: Physiological pain protects the body and its systems from damage, but pathological pain has no obvious biological role. Complementary alternative medicine (CAM) agents are being increasingly studied in the treatment of clinical pain, and some dietary constituents (polyphenol, carotenoids, and fatty acids) and supplements may modify pain pathways. Because these substances modulate neuronal excitability—including the trigeminal pain pathway via various voltage-gated ionic channels and transient receptor potential and ligand-gated channels, dietary constituents could contribute to CAM as therapeutic agents for attenuating orofacial noxious sensory information. This review summarizes the current understanding of the mechanisms by which dietary constituents might attenuate excitability of trigeminal nociceptive neurons implicated in blocking pain, particularly in relation to the authors' recent experimental data, and discusses the development of functional foods and the contribution of dietary constituents in the relief of clinical dental pain without the side effects of nonsteroidal anti-inflammatory drugs.

Keywords: complementary and alternative medicine, nociceptive neurons, nonsteroidal anti-inflammatory drug, transient receptor potential, trigeminal system, voltage-gated channels

Introduction

Some dietary constituents and supplements might affect protective biological mechanisms, such as those in cardiovascular, neural, and anticancer systems [1,2]. Complementary alternative medicine (CAM) therapies such as herbal medicines and acupuncture are often used in pain management, especially after the failure of conventional Western medicine [3-5] or when adverse side effects are a concern [4-7]. Among dietary constituents, substances that contain polyphenol compounds (resveratrol, chlorogenic acids, catechin, and genistein), carotenoids (lutein), and fatty acids (docosahexaenoic acid [DHA] and docosanicoic acid [DA]) could affect peripheral and central nociceptive neuronal pathways, including the trigeminal pain pathway, via voltage-gated ionic (Na⁺, K⁺, and Ca²⁺) channels and transient receptor potential (TRP) and ligand-gated channels (glutamate, opioid, and acetylcholine receptors) [8-30]. Table 1 summarizes the possible molecular receptors [46]. Another study showed membrane hyperpolarization after M2 receptor stimulation-induced generator potential and subsequent initiation of action potentials (Fig. 1).

Physiological pain has evolved to limit biological damage; however, pathological pain has little biological benefit. Dietary constituents might serve as CAMs that attenuate noxious sensory information by contributing to relief of nociceptive and/or pathological pain. Conventional pharmacological agents for pathological pain relief include the classic opioids and nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit cyclooxygenase (COX)-2 cascades [31-35]. However, both these drug classes have numerous side effects, such as stomach ulcer. Dietary constituents might therefore be part of an important alternative treatment plan for pathological pain. This review summarizes the mechanisms by which dietary constituents might modulate nociceptive excitability associated with trigeminal pain, in light of the authors' experimental in vivo data.

In addition, the physiological value of such dietary agents as CAM agents is considered.

Ascending pathways for trigeminal nociceptive information

The trigeminal nociceptive sensory pathway is divided into the lateral and medial systems. Lateral pain conveys information underlying sensory discrimination of pain, including its location, intensity, and quality, while the medial pain system conveys the emotional aspect of pain. Noxious orofacial signals are transmitted via trigeminal ganglion (TG) neurons to second-order neurons in the spinal trigeminal nucleus caudalis (SpVc) and upper cervical (C1-C2) spinal cord [36]. This SpVc/C1-C2 nexus is an important signaling station for trigeminal nociceptive inputs generated by tissue inflammation and damage [36]. SpVc/C1-2 nociceptive neurons comprise nociceptive-specific (NS) and wide dynamic range (WDR) neurons [36]. NS neurons respond only to noxious stimulation of receptive fields and thus possibly send location-related information to higher centers [36]. In contrast, WDR neurons respond to noxious and non-noxious stimulation [37,38]; graded nociceptive stimulation is applied to the most sensitive area of the receptive field, thus inducing increased firing frequency in proportion to stimulus intensity. Therefore, WDR neurons act physiologically to transmit stimulus-intensity information to a higher center. Projection neurons in the SpVc and C1-C2 send axons to the ventromedial posterior (VPM) and medial thalamic nuclei and the parabrachial nucleus (PBN) [37,39], whereby the VPM transmits nociceptive information to primary and secondary somatosensory cortical neurons.

Modulatory mechanism by which dietary constituents modulate trigeminal nociceptive pain

Peripheral mechanism

Mechanical stimulation of peripheral tissues activates TRP ankyrin 1 (TRPA1) mechanotransduction in TG neurons, which in turn evokes generator potentials [40-42]. In vitro and in vivo studies have revealed the potentiatory action of dietary lutein and resveratrol on TRPA1 pathways [27,29] and thus the amplitude of generator potential and subsequent trigeminal ganglia activation. In addition, resveratrol and DHA inhibited generation of action potentials in vitro, depolarizing step pulse-induced voltage-gated Na⁺ currents in primary sensory neurons [15,19,25], whereas voltage-gated K⁺ currents in primary sensory neurons were potentiated by resveratrol and chlorogenic acid [13,30]. These dietary constituents may therefore act as local anesthetic agents in vivo. Recently, the present authors reported that local injection of resveratrol, chlorogenic acid, and DHA dose-dependently inhibited the nociceptive reflex and SpVc WDR neuronal activity [43-45]. Thus, dietary intake of these substances could attenuate excitability of nociceptive TG neurons through mechanical stimulation-induced generator potential and subsequent initiation of action potentials (Fig. 1).

Electrophysiological experiments using a rat skin-nerve preparation indicated that the muscarinic acetylcholine (mACh) M₁ receptor had an inhibitory or desensitizing influence on the peripheral terminal of C-nociceptors [46]. Another study showed membrane hyperpolarization after mAChRs stimulation via activation of low-threshold, voltage-operated K⁺ channels in nucleus raphe magnus (NRM) neurons [47]. The present authors’ recent in vivo electrophysiological and behavioral experiments showed that topical DA reversibly evoked transient mechanical hyperalgesia, presumably via the same mechanism described above in TG neurons [48,49]. Together, these data suggest that DA is a potential therapeutic CAM for treatment of trigeminal nociception (Fig. 1).
Central mechanism

T-type Ca\(^{2+}\) currents in isolated primary sensory neurons can be inhibited by α-lipoic acid (LA) [26]. Therefore, because such a mechanism could act on the earliest point of trigeminal pain pathways, LA might also dampen SpVc excitation via presynaptic signaling that attenuates voltage-dependent Ca\(^{2+}\) channels. Indeed, LA also affects \(^{14}N\)-methyl-aspartate (NMDA) currents in cortical neurons postsynaptically [50]. Because intrathecal administration of NMDA receptor antagonists inhibits nociceptive behavior [51,52], the NMDA receptor signaling system likely contributes to spinal nociceptive transmission. Using extracellular recordings after non-noxious and noxious mechanical stimulation in rats, the present authors noted that intravenous administration of LA suppressed excitability of nociceptive SpVc WDR in vivo [53]. Thus, LA might suppress excitatory synaptic pathways by inhibiting presynaptic Ca\(^{2+}\) channels and postsynaptic glutamate receptor signaling (Fig.1). Accordingly, the present authors recently examined whether a similar effect was elicited after acute intravenous administration

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Table 1 Possible molecular targets for dietary modulation of neuronal excitability in the pain pathway (in vitro)

<table>
<thead>
<tr>
<th>Molecular targets</th>
<th>Dietary constituents (foods)</th>
<th>Effects (references)</th>
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<tbody>
<tr>
<td>Voltage-gated ionic channels</td>
<td></td>
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<tr>
<td>● Na(^{+}) channel</td>
<td>Resveratrol (grape, red wine)</td>
<td>Inhibition (19, 20)</td>
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<tr>
<td></td>
<td>Docosahexaenoic acid (fish oil)</td>
<td>Inhibition (9,10,12,15)</td>
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<td></td>
<td>Eicosapentaenoic acid (fish oil)</td>
<td>Inhibition (11,21,22)</td>
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<td></td>
<td>Genistein (soy bean)</td>
<td>Inhibition (16)</td>
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<td>Catechin (green tea)</td>
<td>Inhibition (25,28)</td>
</tr>
<tr>
<td></td>
<td>Quercetin (apple, onion)</td>
<td>Inhibition (23)</td>
</tr>
<tr>
<td>● K(^{+}) channel</td>
<td>Resveratrol (grape, red wine)</td>
<td>Facilitation (13)</td>
</tr>
<tr>
<td></td>
<td>Chlorogenic acids (coffee)</td>
<td>Facilitation (30)</td>
</tr>
<tr>
<td>● Ca(^{2+}) channel</td>
<td>Resveratrol (grape, red wine)</td>
<td>Inhibition (24)</td>
</tr>
<tr>
<td></td>
<td>Docosahexaenoic acid (fish oil)</td>
<td>Inhibition (10)</td>
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<tr>
<td></td>
<td>Eicosapentaenoic acid (fish oil)</td>
<td>Inhibition (21)</td>
</tr>
<tr>
<td></td>
<td>α-Lipoic acid (spinach, tomato)</td>
<td>Inhibition (26)</td>
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<td>TRP channels</td>
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<tr>
<td>● TRPA1</td>
<td>Resveratrol (grape, red wine)</td>
<td>Inhibition (29)</td>
</tr>
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<td></td>
<td>Lutein (broccoli, spinach)</td>
<td>Inhibition (27)</td>
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<td>Ligand-gated ionic channels</td>
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<tr>
<td>● Glutamate receptor</td>
<td>Resveratrol (grape, red wine)</td>
<td>Inhibition (24)</td>
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<td></td>
<td>Theanine (green tea)</td>
<td>Inhibition (8,14)</td>
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<tr>
<td>● μ-Opioid receptor</td>
<td>Resveratrol (grape, red wine)</td>
<td>Inhibition (17)</td>
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<td></td>
<td>Decanoic acid (palm oil, cheese)</td>
<td>Facilitation (18)</td>
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</tbody>
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**Fig. 1** Possible molecular targets for dietary constituents in alleviating trigeminal pain in vivo. Nociceptive pain: as with local application of resveratrol on peripheral tissues, dietary intake reduces generator potential amplitudes and rates of subsequent action potentials, via mechanical transduction (43). During action potential generation, voltage-gated Na\(^{+}\) currents in trigeminal ganglia are inhibited by resveratrol and DHA applied locally (43,45), while voltage-gated K\(^{+}\) currents in primary sensory neurons are potentiated by resveratrol and chologogic acid (44). Topical application of deacanonic acid also induces mechanical hypalgesia, which in turn suppresses trigeminal ganglia excitability through M\(_1\) mAChR signaling, thereby stimulating membrane hyperpolarization (48,49) and inhibiting action potential firing rates discharged through nociceptive primary afferent fibers to the central terminal and nociceptive neurons in the SpVc. Systemic delivery of LA inhibits Ca\(^{2+}\) currents in presynaptic terminals, while local administration of resveratrol suppresses glutamnergic-activated neurotransmission of SpVc neurons responding to nociceptive mechanical stimulation via the NMDA receptor. Activation of μ-opioid receptor in the presynaptic terminals may decrease neurotransmitter release, which suggests that decreasing excitatory postsynaptic potentials amplitudes to below the action potential threshold blocks a barrage of action potentials conducted to higher centers in the pain pathway, thus attenuating pain perception (53-56). Resveratrol also suppresses synaptic excitability functioning of the SpVc by stimulating descending pain modulation. Glu, glutamate; WDR, wide dynamic range neurons. Inflammatory pain: chronic administration of the dietary constituents resveratrol, lutein, and DHA might attenuate inflammation-induced mechanical inflammatory hyperalgesia, primarily by suppressing SpVc WDR neuronal hyperexcitability via inhibition of peripheral cascades of Cox-2 signaling (64-66). R, resveratrol; Glu, glutamate; WDR, wide dynamic range neurons; TRP, transient receptor potential; Nav, voltage-gated Na\(^{+}\) channel; Kv, voltage-gated K\(^{+}\) channel; Cav, voltage-gated Ca\(^{2+}\) channel; ARA, arachidonic acid; (-) suppression; (+) potentiation; Enk, enkephalin; DHA, docosahexaenoic acid; α-LA, α-lipoic acid; Glu, glutamate; PAG, periaqueductal grey; NRM, nucleus raphe magnus; 5HT, 5-hydroxytryptamine; GABA, γ-amino-butyric acid
of resveratrol and found significant suppression of SpVcWDR neuronal firing after noxious mechanical stimulation in resveratrol-injected rats [54]. In addition, resveratrol significantly suppressed glutamate-stimulated SpVc WDR firing—the relative magnitude of inhibition was similar to that for NMDA iontophoretic application [55]. These findings suggest that resveratrol can attenuate glutamatergic excitation of SpVc neurons through NMDA receptor signaling (Fig. 1). Descending pain modulation systems can also affect ascending nociceptive information related to pain. Specifically, intravenous resveratrol inhibits the nociceptive jaw-opening reflex through μ-opioid receptor signaling [56], while in the periaqueductal gray (PAG), GABAergic neuronal inhibition was reversed by enkephalin binding to μ-opioid receptors [57]. Such disinhibition activates glutamatergic followed by serotonergic neurons in the nucleus raphe magnus (NRM) (the PAG-NRM-trigeminal pathway) [56]. In addition, in vitro resveratrol suppresses currents stimulated through 5-HT3 receptors [58], and conditioning stimulation of peripheral nerve induced 5-HT3 receptor-mediated GABAergic inhibition on the excitability of SpVc neurons responding to noxious stimulation [59, 60]. Together, these findings indicate that excitatory synaptic transmission of the SpVc is suppressed by resveratrol via activation of GABAergic activity mediated by 5-HT3 receptor (Fig. 1).

How do dietary constituents mechanically modulate inflammatory pain?

As shown in Fig. 1, the proinflammatory mediator PGE2 binds to G protein-coupled prostanooid EP receptors. It can also stimulate protein kinase A (PKA) activity in nociceptive peripheral terminals after peripher al inflammation, thus leading to phosphorylation of mechanosensitive TRPA channels and voltage-gated Na+[3] and K+[4] channels and, ultimately, to a decreased threshold for TRPA1 transducer activation and increased peripheral terminal membrane excitability. These events in turn increase the nerve impulse frequency to the SpVc presynaptic central terminals.

Various dietary constituents can inhibit Cox-2 and related inflammatory cytokine activity [35, 61]. The present authors recently tested the hypothesis that intraperitoneally administered dietary constituents could attenuate SpVc neuronal hypersensitivity related to mechanical hyperalgesia induced by complete Freund’s adjuvant (CFA) [62, 63]. In addition, the authors showed that resveratrol, DHA, and lutein provided in the diet inhibited inflammatory mechanical hyperalgesia and associated nociceptive neuronal hyperexcitability induced by CFA, possibly by inhibiting the Cox-2 converting enzyme from arachidonic acid to PGE2 [64-66].

This experimental series showed (i) that the lowered escape threshold for mechanical stimulation in inflamed rats returned to control levels with ongoing administration of dietary constituents, (ii) that dietary components also reversed the high-frequency SpVc WDR discharges elicited by mechanical non-noxious and noxious stimuli, (iii) that dietary constituents returned the spontaneous discharges rates of SpVc WDR neurons as well as the noxious pinch-evoked after-discharge frequency in inflamed rats, and (iv) that control levels of receptive field expansion in inflamed rats were attained [64-66]. Taken together, these findings indicate that resveratrol, lutein, and DHA significantly limited mechanical hyperalgesia induced by inflammation, probably by primary suppression of SpVc WDR neuronal hyperexcitability after attenuated peripheral COX-2 signaling (Fig. 1). Thus, dietary constituents could be used as a potential therapeutic agent on CAM, for prevention of trigeminal inflammatory hyperalgesia.

Inflammation-induced PGE2 facilitates activation of TRPV1 and tetrodotoxin (TTX)-resistant (TTX-R) Na+ channels [19, 32, 67] in sensory terminals. Acutely administered resveratrol inhibits TTX-sensitive (TTX-S) and TTX-R Na+ currents in acutely dissociated dorsal root ganglion (DRG) neurons, while TTX-R Na+ channels are selectively expressed in nociceptive small-diameter trigeminal ganglion via increased TTX-R Na+ currents [69]; therefore, dietary constituents might similarly inhibit excitability of these neurons by suppressing TTX-R Na+ channel sensitization. As shown in Fig. 1, at least some of the peripheral antinociceptive action of dietary constituents is attributable to blocked peripheral sensitization. The undesirable side effects of commonly used analgesic drugs, including NSAIDs, Cox-2 inhibitors, and opioids, have increased interest in CAM agents for treatment of chronic pain [5, 70]. Similarly, the potential effects of diet and dietary supplements on trigeminal pain warrant study [6, 71].

Functional significance of orofacial pain and future research

Individuals undergoing orthodontic procedures commonly develop orofacial pain, both direct tooth pain and pain referred across other areas [72]. However, despite the impact and frequency of such episodes, the physiological mechanism underlying referred pain is unclear [73]. Pain due to tooth movement might be related to post-procedural conditions [74]. Mechanical pressure-induced production of Cox-2-induced proinflammatory mediators can induce inflammatory orthodontic pain [75]. Indeed, Cox-2 production may substantially increase at local inflammation sites such as periodontal tissue [34]. An immunohistochemical study using a rat model of experimental tooth movement showed Cox-2 in the SpVc [73], but not in periodontal tissue, which suggests that local inhibition of Cox-2 is important in preventing and mitigating inflammatory pain associated with orthodontic tooth movement. Therefore, dietary intake of resveratrol, lutein, and DHA might attenuate mechanical hyperalgesia by inhibiting SpVc WDR excitability through the Cox-2 signaling pathway [64-66].

Strong evidence indicates that activation of glial cells of the SpVc, and subsequent production of cytokines, is an important underlying factor in pathological pain [76]. These responses might extend beyond central glial cells to peripheral satellite glial cells. In addition, because peripheral sensitization of trigeminal nociceptors suggests increased neuron-glia interactions [36], the present authors hypothesize that dietary constituents may be potential therapeutic targets for neuron-glia interactions to inhibit trigeminal inflammatory pain.

Trigeminal pain comprises the lateral and medial systems. The lateral pain pathway is thought to be involved in discriminating pain location, intensity, and quality. In contrast, the motivational and affective aspects of pain are associated with emotional and autonomic responses caused by persistent, intense noxious stimuli in the medial system of pain pathways, although recent studies of the effects of dietary constituents on pain mechanisms have mostly focused on lateral pain, which encompasses the sensory-discriminative aspect of pain. Future studies should thus examine how dietary constituents might affect medial pain.

In conclusion, the authors recently reported that dietary constituents may be potential therapeutic CAM agents for alleviating trigeminal pain and inflammatory hyperalgesia via various voltage-dependent ion and ligand-gated channels and the Cox-2 pathways. These findings will aid in the development of functional foods that could help relieve clinical dental pain without the side effects of nonsteroidal anti-inflammatory drugs.

Conflict of interest

The authors declare that they have no competing interest relevant to this study.

References

routed fatty acids modulate sodium and calcium currents in CA1 neurons. Proc Natl Acad Sci U S A 93, 2523-2528.