Journal of Oral Biosciences 61 (2019) 12–15

Contents lists available at ScienceDirect

Journal of Oral Biosciences

journal homepage: www.elsevier.com/locate/job

Pain mechanism of oral ulcerative mucositis and the therapeutic traditional herbal medicine hangeshashinto

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ARTICLE INFO

Article history:
Received 25 December 2018
Received in revised form
24 January 2019
Accepted 29 January 2019
Available online 30 January 2019

Keywords:
Traditional Japanese herbal medicine
Hangeshashinto
Oral ulcerative mucositis
Pain
TRP channels

ABSTRACT

Background: Oral ulcerative mucositis causes severe pain during eating and speaking, resulting in poor quality of life for patients with cancer undergoing chemoradiotherapy. Recently, some basic and clinical studies demonstrated that hangeshashinto, a traditional Japanese herbal medicine, alleviated oral ulcerative mucositis-induced pain. Here, we review a recently revealed pain mechanism underlying oral ulcerative mucositis in a preclinical rat model and the pharmacological analgesic effect of hangeshashinto.
Highlight: In a rat model of experimentally induced oral ulcerative mucositis, the mucosal surface of the ulcerative region is damaged, which increases oral bacterial loading in the mucosa and prostanoid production. Chemotherapeutic drugs exaggerate the pathological condition and cause severe pain. The pain-related TRP channels, TRPV1, TRPA1, and/or TRPV4, mediate spontaneous and mechanical pain in oral ulcerative mucositis models. Swab application of hangeshashinto had a prolonged localized analgesic effect on oral ulcerative mucositis, even in a chemotherapy-treated oral ulcer model. Two ingredients of hangeshashinto, gingerol and shogaol, strongly inhibit voltage-activated sodium channels (though they have agonistic effects on TRPV1 and TRPA1), which confers hyposensitivity to the oral mucosa. Their analgesic effects on oral ulcerative mucositis are accompanied by accelerated delivery of drugs (other saponin-containing herbal extracts) into the ulcerative region.
Conclusion: Elucidation of the pain mechanism of oral ulcerative mucositis and analgesic mechanism of hangeshashinto will allow identification of novel therapeutic approaches against oral ulcerative mucositis-induced pain in patients. The traditional Japanese herbal medicine hangeshashinto is a reliable drug with supporting scientific evidence.

Contents

1. Introduction

Oral mucositis is one of the most common painful oral mucosal lesions and frequently occurs in patients with recurrent aphthous stomatitis, dentures, and orthodontic appliances [1,2]. Such oral

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https://doi.org/10.1016/j.job.2019.01.004
1349-0079/

mucositis-induced pain negatively affects speaking and swallowing, the maintenance of oral hygiene, and the patient's quality of life [3–5]. In patients with head and neck cancer, oral ulcerative mucositis is one of the most serious side effects of chemoradiotherapy and results in severe pain. Sometimes, the extent of the pain forces the delay and/or interruption of cancer therapy [5,6]. To alleviate pain in patients with cancer, lidocaine, a typical local anesthetic drug, has been topically applied to the oral cavity [7–9]. However, the treatment is only effective for a short time and simultaneously induces the loss of touch and taste sensations [8], resulting in loss of appetite in patients. Therefore, long-lasting anesthetic drugs without side effects are required for patients that experience oral ulcerative mucositis-induced severe pain.

Basic and clinical research has demonstrated the effectiveness of the traditional Japanese herbal (Kampo) medicines for this type of pain [10–12]. We previously revealed the pathophysiological mechanism of oral ulcerative mucositis in some preclinical models in conscious rats through the development of a pain assay [13]. This review introduces the elucidated molecular mechanisms of oral ulcerative mucositis-induced pain and the pharmacological mechanism underlying the analgesic effect of the Kampo medicine, hangeshashinto.

2. Pain mechanism in oral ulcerative mucositis

In many previous studies, the topical treatment of acetic acid has been applied to the oral mucosa of rats to induce experimental oral ulcerative mucositis and investigate the pathology and the effects of the drug [10,11,13–16]. The topical treatment on the mucosal surface in the labial fornix region leads to inflammatory cell infiltration and swelling in the treated mucosal region on the day after treatment [15]. On the second day after treatment, oral ulceration is clearly observed, with exposure of the lamina propria due to the destruction of the mucosal surface, which results in considerable permeability to exogenous substances such as oral bacteria, in contrast to the healthy oral mucosa containing a viable epithelial barrier [11,13]. On the same day, prostanoids are upregulated in the mucosal lesions [15,16]. The pathological conditions disappear several days after the acetic acid treatment. In addition, we also developed an oral ulcer model of orthodontic wire-induced mucositis [17]. The model comprises submucosal abscess with traumatic ulcer and is different from the acetic acid-treated model.

To evaluate intraoral pain in conscious rats using traditional nociceptive assays, we developed an intraoral dropping method and a stable intraoral opening method for direct stimulation of the oral mucosa [13]. Following the dropping of pungent solutions (the TRPV1 agonist capsaicin or the TRPA1 agonist allyl isothiocyanate) and pricking of the exposed oral mucosa by von Frey filaments, grooming-like behaviors (mouth rubbing and/or facial wiping) and head withdrawal threshold, respectively, were measured as signs of nociception in rats. By using the novel pain assay system, we evaluated spontaneous and mechanical (touch-induced) pain in oral ulcerative mucositis and revealed the contribution of TRPV1, TRPA1, and/or TRPV4 in some oral ulcer models [13,15,16]. In the acetic acid-treated model, spontaneous pain is induced by persistent TRPA1 activation following prostanoid and/or lipopolysaccharide production [15,18,19]. Importantly, mechanical pain is independent of prostanoid production [15]; thus, the two pain modalities in oral ulcerative mucositis have distinct routes, cyclooxygenase dependent and independent. Mechanical pain is mediated by mechanical hypersensitivity of TRPA1 and/or TRPV4, owing to bacterial toxins (lipopolysaccharide and N-formyl methionine peptides), endothelin, and neutrophil elastase [15,17,20,21].

It is well-known that chemotherapy exaggerates the symptoms of oral mucositis in patients [22]. A clinical study found that chemotherapy-associated leukopenia led to severe oral ulcerative mucositis and pain [23]. Indeed, after the administration of 5-fluorouracil, a representative chemotherapeutic drug, the experimentally induced oral ulcerative mucositis model demonstrated excessive oral bacterial loading due to leukopenia associated with a lack of leukocyte phagocytosis [16]. Furthermore, the chemotherapy-treated model results in more severe spontaneous and mechanical pain. The different mechanisms underlying oral ulcer pain between conventional and chemotherapy-treated oral ulcerative mucositis models are shown in Table 1. It is likely that the switching from TRPA1 to TRPV1 in spontaneous pain and intensiveness to TRPA1 in mechanical pain after 5-fluorouracil administration would be caused by different pathological states, such as high lipopolysaccharide content and/or lack of inflammatory cell infiltration.

Table 1
Summary of pathological status and involvement of TRP channels in conventional and chemotherapy oral ulcerative mucositis-induced pain.

		Oral ulcerative mucositis rat model (Day 2)	
		Acetic acid	5-FU+/Acetic acid
In ulcerative mucosa	Bacterial loading	↑↑	↑↑↑↑
	Prostanoid production	↑↑	↑↑
In blood	Leukocytes	↑↑	↓
Spontaneous pain		TRPA1	TRPV1
Mechanical pain		TRPA1, TRPV4, TRPV1	TRPA1

5-FU; 5-fluorouracil. ↑↑, refer to significant increase compared with naive. ↑↑↑↑, refer to significant increase compared with conventional model (Acetic acid). ↓, refer to decrease but significantly compared with naive [15,16].

3. Analgesic effects of hangeshashinto on oral ulcerative mucositis-induced pain

Kampo medicine was imported from China in the 5th–6th century [24,25] and developed into the individual form of each medicine adapted for Japanese people [12]. The herbal medicines are composed of several plant extracts and are prescribed for suitable patient symptoms. Hangeshashinto, a Kampo medicine, is composed of seven extracts (Coptis Rhizome, Ginseng, Glycyrrhiza, Jujube, Pinellia Tuber, Processed Ginger, and Scutellaria Root) and has been approved by the Ministry of Health, Labor and Welfare of Japan and applied for gastrointestinal diseases and symptoms as a pharmaceutical-grade drug in Japan [12,26,27]. Recent clinical studies have reported that repetitive mouth washing with hangeshashinto reduces oral mucositis scores, including pain symptoms, and improves chemoradiation completion rates in patients with cancer [27–29].

In our previous study that used the oral ulcerative mucositis model induced by acetic acid treatment, swab application (to mimic mouthwash) of hangeshashinto to the ulcerative region alleviated mechanical and spontaneous pain for an extended period (over 60 min) [11]. Similar to the results of clinical studies, sufficient analgesic effects were also found in the 5-fluorouracil-treated oral ulcer model. Unexpectedly, the analgesic effect occurred in only the ulcerative region, and not in the healthy oral mucosa; thus, the Kampo medicine is more suitable drug for patients with oral ulcers than lidocaine, which has a non-specific and short-acting effect (less than 30 min) [8,11,30]. The long-lasting region-specific effect of hangeshashinto is particularly

advantageous as it does not affect the taste and touch sensations in the oral cavity of patients with cancer.

4. Ingredient-based analgesic mechanisms of hangeshashinto

Among the components of hangeshashinto, [6]-gingerol and [6]-shogaol (in the Processed Ginger extract) and isoliquiritigenin (in the Glycyrrhiza extract) exhibit antagonistic effects on voltage-dependent sodium channels (e.g., Na_v 1.8) [10], although [6]-gingerol and [6]-shogaol were reported to weakly stimulate TRPV1 and/or TRPA1 [10,31,32]. Therefore, both ingredients demonstrate inhibitory effects on the generation of action potentials and substance P release in cultured sensory neurons and hyposensitive to mechanical sensitivity in the oral mucosa [10]. As the inhibitory effects on voltage-dependent Na^+ channels are greater than the inductive effects on TRPV1 and/or TRPA1, [6]-shogaol and [6]-gingerol would function as analgesic agents. These findings suggest that these ingredients contribute to the analgesic effects of hangeshashinto on oral ulcerative mucositis-induced pain.

However, the swab application of [6]-gingerol and [6]-shogaol on the ulcerative region did not exert analgesic effects, even at doses that were estimated to be present in an effective dose of hangeshashinto [10], which indicated that the ingredients have low permeability into the oral mucosal tissue. Therefore, we considered the possibility of another compound as a partner for the delivery of hangeshashinto. Triterpenoid glycosides (saponins) are known to introduce extracellular substances into the cell membrane owing to their surface active characteristics [33]. In hangeshashinto, ginsenosides (from the Ginseng extract) and glycyrrhizin (from the Glycyrrhiza extract) contain an abundance of saponins. Indeed, the swab application of [6]-gingerol and [6]-shogaol, in combination with Ginseng extract, had good analgesic effects on oral ulcerative mucositis-induced pain [10]. Hangeshashinto appears to be composed of both bio-effective analgesic and drug-delivery components.

5. Clinical significance of the herbal medicine for oral diseases/disorders

Recently, many in vivo and in vitro studies of the potential therapeutic properties of traditional Japanese herbal medicines for oral diseases and disorders have been conducted [34]. Hangeshashinto has been reported to exhibit antibacterial and anti-inflammatory effects in vitro, in vivo, and in clinical studies [12,35–38], in addition to the analgesic effects described in our previous studies [10,11]. In Japan, approximately 85%–90% of clinical practitioners prescribe several herbal medicines to control the oral pain associated with dental caries, pulpitis, and periodontal diseases [24,34,39]. For the treatment of oral ulcerative mucositis, orengedokuto, inchinkoto, and orento are frequently used, as well as hangeshashinto [12]. The long history of these medicines confirms their safety in clinical usage.

6. Conclusions

Oral ulcerative mucositis-induced pain is unendurable and intractable for patients with cancer. Hangeshashinto is useful as an effective drug in treating such a severe pain. Further studies on the pathophysiological and therapeutic mechanisms of oral ulcerative mucositis are required. We believe that further exploration will be of great help to patients that experience oral ulcerative mucositis-induced pain.

CRediT authorship contribution statement

Suzuro Hitomi: Conceptualization, Data curation, Formal analysis, Funding acquisition, Validation, Writing - original draft, Writing - review & editing*. **Izumi Ujihara:** Validation, Writing - review & editing. **Kentaro Ono:** Conceptualization, Funding acquisition, Supervision, Validation, Writing - review & editing.

Acknowledgements

We thank the members of the Division of Physiology, Department of Health Promotion, Kyushu Dental University and Research Laboratories, Kampo Scientific Strategies Division, Tsumura & Co. This work was supported by Tsumura & Co. (Japan) and Grant-in-Aid for Young Scientists (B) from the Ministry of Education, Culture, Sports, Science and Technology (Japan Society for the Promotion of Science KAKENHI Grant nos. 25861760 and 15K20377) (Japan).

Conflict of interest

The authors declare no competing financial interests.

Ethical statement

Ethical approvals are not required in this review.

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