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Review

Oral malodorous gases and oral microbiota: From halitosis to carcinogenesis

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ABSTRACT

Background: Since most oral malodor originates from microbial activities in the mouth, the role of microorganisms in producing malodorous gases has been clarified by numerous studies, accompanied by the development of analytical techniques for treatment of halitosis.
Highlight: Oral microorganisms should be controlled to prevent aspiration pneumonia, especially for elderly perioperative patients. Malodorous gases from the mouth can be an indicator of oral or systemic conditions among patients in intensive care units. Recently, malodorous gases originating from oral microorganisms have been reported as a causal factor in carcinogenesis.
Conclusion: Further analysis of oral malodor might be useful in accessing the risk of aspiration pneumonia and oral cancer.

Contents

1. Introduction

Oral malodor in humans has long been a major health concern. Communication is essential in civilized society, but bad breath hinders it. In spite of its importance, oral malodor is usually not detected by patients themselves; this difficulty can produce anxiety in patients suffering from halitosis [1]. Objective analytical techniques based on an organoleptic test are necessary, and have been developed to measure malodorous gases for diagnosis and treatment of halitosis [2–4]. As teeth and tongue cleaning, mouthwash rinsing, and periodontal therapy can control oral malodor, most of which originates from microbial activities in the mouth [5], the role of oral bacteria in saliva, tongue coating, and periodontal pockets has been widely studied in regard to oral hygiene.

Studies have revealed that the oral cavity is a reservoir of bacteria known to cause nosocomial pneumonia, and that it is necessary to control these bacteria in hospitalized patients, such as

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those in intensive care units (ICU) [6,7]. Oral malodor may serve as a useful assessment tool for evaluating patients in critical condition. Epidemiological studies have found that poor oral hygiene is associated with an increased risk of squamous cell carcinoma of the head, neck, and esophagus [8,9]; some have shown that the association may be causal [10,11]. Malodor originating in the oral cavity is an indicator of metabolic output of oral microbial communities as a whole. It is possible that oral malodorous gases indicate not only halitosis but also pathogenicity of oral microbiota.

2. Dental plaque as a risk factor for aspiration pneumonia

Oral microbiota has been shown to be an important risk factor for aspiration pneumonia [6], nosocomial bacterial pneumonia, and chronic obstructive pulmonary diseases [12]. Using molecular genotyping, El-Solh et al. investigated the association between dental plaque colonization and lower respiratory tract infections in elderly hospitalized patients and suggested that aerobic respiratory pathogens colonizing in the dental plaque may be an important reservoir for hospital-acquired pneumonia in this population [13]. Didilescu et al. indicated that dental plaque in patients with chronic lung diseases often serves as a reservoir for the bacteria known to cause nosocomial pneumonia in patients with chronic lung diseases [14]. Oral care is essential for preventing pneumonia in institutionalized elderly patients [15], and ventilator-associated pneumonia in ICU patients [7]. Malodor has also been suggested as an indicator of oral conditions in the oral assessment of patients in ICUs [16].

3. Role of oral microorganism in halitosis

There is a long history of studying the origins of and treatment for oral malodor in humans. Hippocrates recommended using a mouthwash for maintaining a pleasant oral odor. He noted that offensive oral odor was related to dark, unhealthy gingiva, and suggested that the malodor would vanish in healthy gingiva [17]. Japanese woodblock prints, known as ukiyoe, showed ordinary people in the 19th century using wooden toothbrushes and tongue scrapers for oral hygiene [18]. In 1970, with the development of gas chromatography, it was confirmed that hydrogen sulfide and methyl mercaptan emanate an offensive putrid odor, which accounts for approximately 90% of the total sulfur content of mouth air [19]. Tonzetich and Ng's study of cleaning both the teeth and the dorso-posterior surface of the tongue indicated that both dental plaque and the tongue were important sources of oral malodor [20].

Oral malodor is strongest and most objectionable in the morning, following the absence of frequent saliva washing that occurs during sleep. The pH of plaque in the morning is at its highest level, and oral alkalinity favors oral malodor formation [21]. Thicker plaque and lower salivary oxygen levels are key to the development of large zones of anaerobiosis, which contributes to the formation of oral malodor [21]. In 1990, a study of subgingival microbiotas sampled from the periodontal pockets of patients showed the formation of various volatile sulfur compounds in human serum [22]. Hydrogen sulfide was found to be the predominant volatile compound, but methyl mercaptan had also formed in significant amounts. Only traces of dimethyl sulfide and dimethyl disulfide were detected. Numerous species of microorganisms produce malodorous oral gases; as many as 82 species produce hydrogen sulfide from cysteine, and as many as 25 species produce methyl mercaptan from methionine [23]. However, it is not only microorganisms, but also the amount of tongue coating and gingival fluid from periodontal pockets, which are factors that enhance the production of volatile sulfur compounds in patients with periodontal disease [24]. Further, there is more than one point of origin for oral malodor: a study of 260 patients in a multidisciplinary breath-odor clinic reported that 87% of oral malodor originates from microbial activities in the mouth, and 8% from the ears, nose, and throat [5].

Considering the technological advances in culturing and identifying the microorganisms populating periodontal pockets, the dorsal tongue surface presents different challenges compared with other oral sites, as the majority of organisms found on its surface are either uncultivable or unidentifiable using traditional procedures [25]. Using culture-independent molecular methods for obtaining 16S rRNA sequences, Kazor et al. clarified the diversity of bacterial populations on the tongue dorsa both of patients with halitosis and of those that were healthy [26]. In the healthy subjects, *Streptococcus salivarius* was by far the predominant species, but was typically absent from subjects with halitosis. Overall, their study found that the predominant microbiota on the tongue dorsa of healthy subjects was different from that on the tongue dorsa of subjects with halitosis. However, due to its complexity, the characteristics of microbiota on the tongue dorsa and its relationship with oral malodor remain unclear. Washio et al. focused on oral malodor in patients without periodontitis or caries, and found that the predominant bacteria producing hydrogen sulfide were not periodontitis-related bacteria but rather indigenous bacteria of the oral cavity, such as *Veillonella* and *Actinomyces* [27]. The relationship between oral malodor and the composition of indigenous bacteria in saliva has also been studied by Takeshita et al. using terminal-restriction fragment length polymorphism [28]. They divided the bacterial compositions of 240 patients into 4 groups, using 2 different fluorescent dyes (6-carboxyfluorescein and hexachloro-fluoresceine). The study showed that differences in the bacterial colonization pattern were significantly associated with the intensity of oral malodor independent of other variables, including 2 major halitosis-inducing factors: an increase in tongue coating and periodontal disease. These results suggested that, except for periodontal disease-associated cases, oral malodor was a symptom based on the characteristic occupation of indigenous oral bacterial populations, rather than solely on bacterial overgrowth due to poor oral hygiene.

Indigenous oral bacteria in the tongue coating, such as *Veillonella*, have been identified as the main producers of hydrogen sulfide, but the metabolic properties of its production have not been fully understood. Washio et al. investigated the production of hydrogen sulfide from L-cysteine by growing cells, resting cells, and cell extracts of oral *Veillonella* species, as well as the effects of oral environmental factors, including pH and lactate [29]. The production of hydrogen sulfide was increased by lactate in the resting cell suspension but not in the cell extract, suggesting that it is caused by lactate activity; not the enzyme itself, but rather the process occurring prior to L-cysteine degradation, such as the incorporation of L-cysteine across the cell membrane. Cell extracts were found to have various enzymatic activities that resulted in production of hydrogen sulfide from L-cysteine, such as cystathionine β-synthase and cystathionine γ-lyase. Ammonia was also produced by all the *Veillonella* species in the metabolic pathway, resulting in the production of hydrogen sulfide.

Sulfur compounds are also produced by periodontitis-associated bacteria. *Porphyromonas gingivalis*, *Treponema denticola*, and *Fusobacterium nucleatum* produce hydrogen sulfide from L-cysteine, and methyl mercaptan from L-methionine [23]. Methyl mercaptan is produced from L-methionine by the enzymatic action of L-methionine-α-deamino-γ-mercaptomethane-lyase (METase), which catalyzes the α, γ-elimination of L-methionine to produce α-ketobutyrate, methyl mercaptan, and ammonia [30,31]. The *mgl* genes encoding