Role of Oxidative Stress on Human Vocal Pathologies

Subjects: Otorhinolaryngology

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Keywords: oxidative stress ; voice ; vocal fold ; antioxidant

1. Introduction

The voice is essential in human life not only as a communication tool but also for vocal arts such as singing. The voice is produced by the vibration of the vocal folds located in the voice box (larynx) [1][2][3]. The vocal folds are a pair of mucosae about 1.5 to 2 cm in length [3]. They abduct during respiration to open the glottis and adduct during production of voice to close the glottis. The vocal folds vibrate via the air flow during exhalation. The vocal fold consists of mucosa and vocalis muscle. The mucosa is only 1 mm thick but has three layers: the superficial layer of the lamina propria (SLP) and intermediate and deep layers [1][2][3]. The intermediate layer is composed of elastic fiber, and the deep layer is supported by collagen fiber. The intermediate and deep layers form the vocal ligament. The vocal ligament has not been observed in any mammal except for humans [4]. It does not exist even in human childhood. It is developed with age and finally matures during puberty when voice mutation is completed [5][6][7]. The role of the vocal ligament is still unclear, but it is suggested that the ligament is beneficial during high-pitch phonation to support the high tension of the mucosa like a high-pitch string of a guitar. This may be one of the reasons for the wide pitch range of the human voice. The vocalis muscle provides a firm scaffold by muscular contraction. The SLP has rare fibrous proteins but contains a range of amorphous substances including glycosaminoglycan (GAG), proteoglycan, and adhesive molecules [8][9]. Hyaluronic acid (HA) is one of the GAGs and has been considered as the most important molecule that is essential in maintaining ideal vibration of the mucosa. Indeed, it was revealed that the vocal fold did not vibrate after HA was completely removed from the vocal fold mucosa [8]. Thus, the SLP is pliable and the center part of vibration. The SLP vibrates in super-rapid motion as fast as 100 cycles per second in men, 200 cycles in women, and up to 800 cycles in soprano singers. This vibratory function is typical for the vocal fold mucosa, and there is no other mucosa that can vibrate like it. The vibration of the SLP is supported by the contraction of the vocalis muscle. This structure is called "cover body theory" [2], in which the vocalis muscle serves as the body and the SLP vibrates as the cover.

2. Role of Oxidative Stress on Vocal Pathologies

Vocal fold pathologies include polyp, nodule, cyst, and Reinke's edema (RE) [10][11][12][13]. A vocal fold polyp is usually a unilateral lesion that occurs as a result of focal hemorrhage inside the mucosa. Loud phonation or strong coughing can cause the formation of a polyp. Vocal fold nodules are bilateral lesions that occur at the anterior one third of the vocal fold, called the "striking zone" because it is exposed to the maximum contact pressure during vocal fold vibration. Chronic injury creates a small bilateral bump. Women and children are susceptible to developing vocal fold nodules because the pitch of vibration of their voices is high, which results in frequent injury of the striking zone. Vocal fold cysts are created inside the SLP after injury to the mucosa, possibly because the epithelium at the injured site moves inside the SLP during wound healing, creating the cyst wall. RE is featured with edema in the SLP, which is usually caused by chronic inflammation due to smoking. These pathologies are caused by inflammation or injury to the vocal fold mucosa, and it is suspected that ROS may have an important role in the pathogenesis of these pathologies. Indeed, there have been several studies including clinical studies that suggest the pathogenic contribution of oxidative stress on vocal fold pathologies.

Branski et al. [14] reported excessive accumulation of ROS in Reinke's edema in human patients. They examined the effects of cigarette smoke exposure to the vocal fold tissue using viable porcine vocal fold and human vocal fold fibroblasts. Cigarette smoke condensate was applied to both tissues and cells, and the results indicated that transepithelial resistance was preserved; however, the gene expression of cyclooxygenase 2 (COX-2) and its downstream

lipid mediator prostaglandin E2 (PGE2) were upregulated by cigarette smoke exposure. It was suggested that cigarette smoke initiates an inflammatory response in vocal fold fibroblasts, but the vocal fold mucosa may have a durable epithelial barrier function.

Alper et al. [15] also exposed freshly excised, viable porcine vocal fold epithelium to hydrogen peroxide for 2 h and reported that exposure to ROS did not significantly alter transepithelial resistance, although a small trend for a decreased concentration of epithelial junctional complex protein was observed. These findings indicate that oxidative stress can alter the vocal fold epithelial function, while the vocal fold has some antioxidant barrier function. RE may be the consequence of the balance and interaction between ROS and antioxidative function in the vocal fold.

Gugatschka et al. [16] performed proteomic analyses of human vocal fold fibroblasts cultured in a medium conditioned with cigarette smoke extract to reveal the mechanism of Reinke's edema. The proteomic analyses revealed that cigarette smoke increased the quantity of proteins involved in oxidative stress responses, and genes linked to ROS were enriched in the cigarette-smoke-induced proteins. Furthermore, they found downregulation of genes of fibrillar collagen, COL1A1 and COL1A2, and upregulation of UDP-glucose 6-dehydrogenases, an inhibitor for the biosynthesis of hyaluronic acid, which means increased deposition of HA in RE. It was suggested that RE may be created by an increase in HA and decrease in collagen fibrils via oxidative stress responses.

"Laryngitis" is the term widely used for inflammation of the larynx, and it is caused by viral or bacterial infection, smoking, laryngopharyngeal reflux, and air pollution. Particulate matter (PM) is a major component of air pollution that can affect the airways, including the vocal fold. Recently, the relationship between laryngitis and PM was reported in a few epidemiological studies [17], but the pathophysiology was unclear. Choi and Kim [18] examined the effects of PM exposure on human vocal fold fibroblasts using an in vitro study. They showed that ROS was significantly increased by the exposure to PM using a dichloro-dihydro-fluorescein diacetate (DCFH-DA) fluorescent dye probe with significant increases in 4-HNE, a marker for lipid peroxidation, and 8-OHdG, a marker for oxidative DNA damage, in immunohistochemical examinations. They also found a significant increase in AhR, an important inflammatory modulator, and CYP1A1 with significant increases in IL-6 and IL-8, the pro-inflammatory cytokines. These findings indicate that PM induces ROS formation and pro-inflammatory cytokines via the AhR-CYP1A1 pathway and causes lipid peroxidation and DNA damage. It is suggested that the ROS-related cell damage and inflammatory response in vocal fold fibroblasts may be a mechanism underlying chronic laryngitis.

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