ER Stress with Rhinologic Diseases

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The endoplasmic reticulum (ER) stress has already been correlated with various diseases through many studies. In the rhinologic field, the relationship between ER stress in obstructive sleep apnea (OSA) associated with chronic intermittent hypoxia (CIH) and inflammatory diseases such as chronic rhinosimusitis (CRS) or allergic rhinitis (AR) has been relatively studied. The role of ER stress in the development of AR is related to Type 2 allergic immune responses, similar to that in asthma, and some are also related to non-Th2 immune responses. ER stress may be involved in various pathways that cause chronic inflammation in CRS. CIH—the main pathological mechanism of OSA—induces ER stress that impacts the heart, brain, and liver to increase OSA-related morbidity. Therefore, targeting the pathophysiological mechanisms in diseases such as AR, CRS, or OSA by appropriately managing ER stress could be utilized as new therapeutic strategy.

Endoplasmic reticulum stress chronic rhinosinusitis allergic rhinitis obstructive sleep apnea

1. Allergic Rhinitis

Type 2 allergic immune responses are typically characterized by eosinophilic inflammation accompanied by increases in type 2 cytokines such as interleukin (IL)-4, IL-5, and IL-13 in affected tissues and blood. These responses are closely associated with various allergic diseases, including allergic rhinitis (AR), a hallmark of which is the presence of serum antigen-specific immunoglobulin E (IgE) indicative of adaptive immunity involving type 2 helper T cells (T_H2 cells) [1].

The allergic response begins at the interface between the external environment and the epithelium and subsequently involves diverse cell types at all levels of innate and adaptive immunity. During these processes, cells produce large amounts of secretory proteins to defend themselves against endogenous and exogenous threats and/or to efficiently communicate with other cell types to generate an organized immune response. Thus, proper functioning of the ER and maintenance of protein homeostasis is critical for these cells. In these processes, the influence of ER stress is not restricted to protein folding, but instead can intersect with immunity at many levels, thereby leading to complex chronic inflammatory diseases such as allergy. Before T cells involved in various allergic disease endotypes can be activated, the allergen must be recognized by antigen-presenting dendritic cells (DCs) and presented to T cells in draining lymph nodes. Epithelial cells are known to be key modulators in controlling DC activation through release of cytokines and endogenous associated molecules. Given the role of epithelial cells as the first line of defense, diverse coexistent environmental insults may also converge on epithelial-DC interactions [2]. For example, inflamed airway epithelial cells exhibit overt signs of ER stress, and bronchial epithelial XBP-1 has been reported to mediate inflammation-induced ER/Ca^{2+} store expansion, which amplifies

Ca^{2+}-dependent secretion of cytokines [3][4]. Thus, ER stress and the UPR pathway may be central players in the regulation of epithelial-DC interactions, which are crucial for the initiation and amplification of allergic response in the respiratory tract. In addition, XBP1 plays a pivotal role in the terminal differentiation of B cells into highly secretory plasma cells by mediating expansion of the ER and synthesis of proteins required for antibody production and secretion [5]. Moreover, the IRE1α-XBP1 arm of the UPR is thought to be important in the early developmental stage of B cells and terminal differentiation of effector $CD8^+$ T cells [4][6]. Notably, considering that XBP-1 mRNA in naïve B cells is uniquely induced by IL-4, this arm of the UPR may be particularly important in the type-2 allergic response [7]. Additionally, differentiation of eosinophils—a subset of granulocytes—from myeloid cell progenitors is uniquely dependent on the IRE1α-XBP1 pathway, and deletion of XBP1 results in massive defects in eosinophil maturation [8]. Moreover, macrophages are known to connect cell surface innate toll-like receptor (TLR) signaling with intracellular IRE1α-XBP1 pathway-mediated secretion of pro-inflammatory cytokines, thereby linking the ER and UPR pathway to innate effector function in macrophages [9]. Concurrent with this, TLR signaling suppresses the ATF4-CHOP-mediated cellular apoptotic pathway to effectively coordinate the innate function of macrophages [10]. Table 1 summarizes reports investigating the relationship between AR and ER stress. A recent in vitro study expanded on these observations in a primary cultured human nasal epithelial cell model of allergic rhinitis caused by the house dust mite (HDM). These researchers used HDM as an allergen at a concentration sufficient to induce an allergic reaction in primary cultured human nasal epithelial cells isolated from two non-asthmatic subjects. Cells from both subjects exhibited increases in p-IRE, as well as increases in the ER chaperone BiP, GRP94, and ER protein 57 (ERp57) 72 hours after exposure to HDM. Expression of the ER stress transducer ATF6α and the downstream transcriptional effector CHOP were also increased after HDM exposure. Allergen exposure was accompanied by activation of caspase-3 to varying degrees in primary human nasal epithelial cells. The authors of this study suggested that HDM induces ER stress in airway epithelial cells and that ATF6α and ERp57 play a significant role in the development of cardinal features of allergic airways disease, such as AR [62].

Table 1. Studies assessing the association between rhinologic diseases and ER stress.

	Associated Diseases	Study Design	Species and/or Tissue Type	Detection Method	Target Gene(s) or Pathway(s) Associated with ER Stress	Results/Conclusions
Sidra M Hoffman, et al. [11]	AR (induced by HDM)	In vitro cells study	Cultured primary human nasal epithelial cells	Western blotting, luminescence assay	p-IRE, GRP94, BiP, ERp57, ATF6, CHOP, caspase-3	Seventy-two hours after exposure to HDM, cell derived from subjects exhibited increases in p-IRE as well as increases in the ER chaperone BiP, GRP94, and ERp57. Expression of the ER stress transducer ATF6α and

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						downstream transcriptional effector CHOP was also increased after HDM exposure. Allergen exposure significantly activated caspase-3 to varying degrees in primary human nasal epithelial cells.
Kim YM, et al. [12]	CRSwNP	In vivo (case-control) and in vitro cell line study	Human nasal epithelial cell line	Immunohistochemical staining, Western blotting	BiP, p-eIF2α, IRE1α	SEB-positive cells were more frequent, and production of ROS was greater in the epithelial layer of EPs than in NEPs or control tissue. SEB was strongly detected in tissues from patients with CRSwNP. Induction of BiP and $p47^{phox}$ was significantly increased in EPs compared with NEPs or control mucosa. In RPMI 2650 cells, SEB-induced BiP was reduced by pretreatment with a ROS scavenger.
Lee HM, et al. [13]	CRS	In vitro study	Human (NP, IT)/A549 cell lines, PNECs	RT-PCR, immunofluorescence, Western blotting	XBP-1, BiP	TGF-β1 increased the expression of EMT markers (E-cadherin, fibronectin, vimentin, and α-SMA) and ER stress markers (XBP-1s and BiP), an effect that was blocked by 4-PBA or PP2 treatment. 4-PBA and PP2 also blocked the effect of TGF-β1 on migration of A549 cells and

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						suppressed TGF-β1–induced expression of EMT markers in PNECs and organ cultures of the inferior turbinate.
Ding W, et al. [14]	OSA (CIH)	Animal model study (case-control)	Rat	RT-PCR, Western blotting	BiP, CHOP, p-IRE1, XBP-1, pro-ATF6, PERK, eIF2α, caspase-3, caspase-9, caspase-12	Addition of Ad increased LVF in CIH model rats (CIH + Ad group) compared with the CIH-only group. The percentage of apoptotic cells and levels of cleaved caspase-3, -9, and -12 was significantly higher in the CIH-only group compared with normal control and CIH + Ad groups. Protein Expression of cleaved caspase-3, caspase-9, and caspase-12 proteins validated TUNEL results.
Zhou X, et al. [15]	OSA (CIH)	Animal model study (case-control)	Rat	Western blotting	Bax, caspase-3, cleaved caspase-12, ATF6, IRE1, BiP, CHOP	Significantly lower levels of oxidative stress, apoptosis, and ER stress were detected in the CIH + PAG group compared with the CIH-only group.
Bourdier G, et al. [16]	OSA (CIH)	Animal model study (case-control)	Rat	Western blotting	p-eIF2α, eIF2α, ATF4, cleaved caspase-3, ATF6, p-PERK, PERK,	CIH induced cardiac proapoptotic ER stress, characterized by increased expression of BiP, p-PERK, ATF4, and CHOP. CIH-induced myocardial apoptosis was confirmed by

	Associated Diseases	Study Design	Species and/or Tissue Type	Detection Method	Target Gene(s) or Pathway(s) Associated with ER Stress	Results/Conclusions
					CHOP, BiP	increased expression of cleaved caspase-3. These CIH-associated proapoptotic alterations were associated with a significant increase in infarcts. HIT prevented both CIH-induced proapoptotic ER stress and increased myocardial infarct size.
Belaidi E, et al. [17]	OSA (CIH)	Animal model study (case-control)	Mice	RT-PCR, Western blotting	BiP, p-eIF2α, eIF2α, p-PERK, PERK, ATF4, CHOP, cleaved caspase-3, ATF6, HIF-1α	CIH induced an increase in ER-Ca^{2+} content, ER stress markers and HIF-1α activity in mice, accompanied by an enhanced infarct size. CIH failed to increase infarct size in HIF-1α–deficient mice. TUDCA totally abolished the IH-induced increase in HIF-1α activity and infarct size.
Hou Y, et al. [18]	OSA (CIH)	Animal model study (case-control)	Mice	ELISA, Western blotting	Cleaved caspase-3, cleaved caspase-9, BiP, PERK, ATF6, IRE1, CHOP, cleaved caspase-12, eIF2α, JNK	TUDCA inhibited CIH-induced ER stress in the liver, as evidenced by decreased expression of BiP, unfolded protein response transducers, and ER proapoptotic proteins.
Cai XH, et al. [19]	OSA (CIH)	Animal model study	Rat	qPCR, Western blotting	BiP, ATF4, ATF6,	Apoptosis was increased and phosphorylation of

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labeling; Bax, BCL2-associated X; PAG, DL-propargylglycine; HIT, high intensity training; HIF-1α, hypoxia inducible factor-1α; TUDCA, tauroursodeoxycholic acid; ELISA, enzyme-linked immunosorbent assay; JNK, c-Jun N-terminal

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		(case-control)		[21]	XBP-1, CHOP	PERK and IRE1 was upregulated in CIH groups. Sal prevented activation of CHOP throughout hypoxia/reoxygenation exposure.
Perrini S, et al. [20]	OSA (CIH)	Case-control study	Human	RT-PCR	ATF4, CHOP, ERO-1	Adipose tissue mRNA levels of ER stress markers (ATF4, CHOP, ERO-1) were decreased only in the therapeutic CPAP group compared with non-OSA and subtherapeutic CPAP groups.

Chronic rhinosinusitis (CRS) is a very complex inflammatory disease that occurs in the nasal cavity and paranasal sinuses. It is traditionally categorized according to the presence of nasal polyp into CRS with nasal polyp (CRSwNP) and CRS without nasal polyp (CRScNP). Various pathological mechanisms are known to contribute to the incidence and aggravation of CRS. Table 1 summarizes reports investigating the relationship between CRS and ER stress. Studies have shown that *Staphylococcus aureus* exotoxins (SEs; SEA, SEC1-C3, SED) and *S. aureus* enterotoxin B (SEB) act as superantigens that affect the promotion of CRS. One study reported significantly more SEB-positive cells and higher production of ROS in the epithelial layer of eosinophilic polyps (EPs) compared with non-eosinophilic polyps (NEPs) or control tissue. The induction of BiP and p47phox (also called neutrophil cytosol factor 1 [NCF1]) was also increased significantly in EPs compared with NEPs or control mucosa. These authors also strongly detected SEB in tissues from patients with CRSwNP, and further showed that SEB induced ER stress responses in RPMI 2650 cells, a human nasal epithelial cell line. In RPMI 2650 cells, BiP elevation by SEB was reduced by pretreatment with a ROS scavenger. The authors suggested that SEB may induce ER stress via ROS production in CRSwNP, and that SEB-induced ER stress may play an important role in the pathogenesis of nasal polyposis [12].

Another study reported that 4-phenylbutylic acid (4-PBA), a chemical chaperone of ER stress, acts via the c-Src pathway to inhibit tumor growth factor-β1 (TGF-β1)-induced epithelial-mesenchymal transition (EMT) in the upper respiratory tract tissue. EMT, a biological process in which a polarized epithelial cell is transformed into a cell with a mesenchymal phenotype, characterized by enhanced mobility and invasiveness and increased production of extracellular matrix (ECM) components. The proto-oncogene product Src, a non-receptor tyrosine kinase that phosphorylates tyrosine residues on proteins, has been proposed as a possible target of the UPR in the induction of EMT. TGF-β1 is a multifunctional peptide that causes EMT in the airway epithelium and nasal tissues. It is

known that EMT is causally linked to CRS and disease recalcitrance, and the role of ER stress and c-Src in TGF-β1–induced EMT has been investigated based on this relationship. The authors of this investigation reported that expression of the EMT markers E-cadherin, vimentin, fibronectin, and α-SMA was increased in NPs compared with that in inferior turbinates. TGF-β1 increased the expression of EMT markers and ER stress markers (XBP-1s and GRP78), an effect that was blocked by treatment with 4-PBA or PP2 (also known as Src and RIP2 kinase inhibitor) in A549 cells, primary nasal epithelial cells (PNECs), and organ cultures of the inferior turbinate. Also, 4-PBA and PP2 were also shown to block the effect of TGF-β1 on migration of A549 cells and suppress TGF-β1–induced expression of EMT markers in PNECs and organ cultures of the inferior turbinate. These results suggest an important role for ER stress and diverse roles for TGF-β1 in CRS [13]. In summary, ER stress may be involved in various pathways that cause chronic inflammation in CRS.

3. Intermittent Hypoxia and Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a disorder in which all or a part of the upper respiratory tract, such as the nasal-oral-pharyngeal-laryngeal region, is partially or completely closed during sleep, resulting in repetitive hypopnea or apnea. This repetitive obstruction of the respiratory tract results in decreased oxygen levels in the blood, frequent sleep fragmentation and various additional complications, including cardiovascular impairments and dementia. In particular, intermittent hypoxia (IH), which occurs repetitively as part of this process, is closely associated with ER stress, a relationship that has been the subject of study. One such study investigated the preventive effect of adiponectin (Ad)-mediated suppression of ER stress on chronic IH (CIH) injury in the rat myocardium. Ad, a circulating cytokine derived from white adipose tissue and cardiomyocytes, has been suggested to exert cardioprotective effects by virtue of its anti-inflammatory, anti-atherogenic, anti-hypertensive, and insulin-sensitizing properties. It has also been reported that Ad levels in plasma are decreased in OSA patients compared with healthy controls. Hence, the authors of this study investigated whether ER stress is mechanistically related to the occurrence of repetitive CIH and whether Ad exerts protective effects on cardiac function in rats. They found that left ventricular function (LVF) was improved in CIH model rats after addition of Ad (CIH + Ad group). ER stress was shown to act through CHOP and BiP, which were significantly increased in the CIH-only group, to affect this process. IRE1, XBP-1, PERK, eIF2α, and ATF6 were also increased in the CIH-only group compared with normal controls—increases that were mitigated by addition of Ad. It was further shown that the percentage of apoptotic cells and the prevalence of cleaved caspase-3, -9, and -12 were significantly higher in the CIH-only group than in normal control CIH + Ad groups. Taken together, these observations suggest that cardiac function is depressed by ER stress-induced apoptosis and protected by Ad-mediated inhibition of ER stress [14]. Moreover, another study reported that DL-propargylglycine (PAG), a known effective inhibitor of cystathionine γ-lyase (CSE)-synthesized hydrogen sulfide (H_2S), protects against myocardial injury in the context of ER stress-induced cardiac dysfunction in the CIH state in rats. Endogenous H_2S plays an important role in maintaining cardiovascular functions, and exogenous H_2S exerts protective effects against myocardial injury induced by various cardiovascular diseases. Predictably, inhibiting the generation of endogenous H_2S has opposite effects. Among the findings of this study was that pretreatment with PAG significantly improved cardiac function in CIH model rats (CIH + PAG group) compared with the CIH-only group. Moreover, levels of oxidative stress, ER stress and apoptosis were significantly lower in

the CIH + PAG group compared with the CIH-only group [15]. In another study in rats that addressed cardiovascular morbidity, protein expression of the proapoptotic ER stress markers, BiP, p-PERK, ATF4 and CHOP, were increased in CIH. Increases in cleaved caspase-3, an apoptosis marker, have also been shown to cause myocardial apoptosis—an IH-associated proapoptotic alteration that correlates with infarct size. In addition, application of high-intensity training in rats was reported to reduce IH-associated proapoptotic ER stress and infarct size [16]. Similarly, ER stress markers and hypoxia inducible factor-1α (HIF-1α) were increased in CIH mice, effects that were also correlated with increased infarct size. HIF-1α is known to be a factor involved in the life or death of cardiomyocites, similar to ER stress, and IH has been reported to not increase the size of infarction in mice genetically deficient in HIF-1α. Additionally, administration of tauroursodeoxycholic acid (TUDCA), a known inhibitor of ER stress, suppressed the enlargement of infarct size in these mice [17]. Taken together, these observations suggest that ER stress is a significant detrimental factor in the essential pathology of patients with OSA, the cardiovascular morbidity associated with CIH. Therefore, if the ER stress response is properly regulated in OSA patients or the factors that suppress ER stress are appropriately managed, the prediction is that cardiovascular morbidity will be decreased.

TUDCA, which is known to suppress ER stress, is also reported to prevent liver damage in mice exposed to CIH. In particular, TUDCA inhibited the dissociation between GRP78 and PERK, resulting in reduced ER stress-mediated cell death [18]. Specifically, administration of TUDCA attenuated pathological changes in the liver, reduced serum alanine aminotransferase and aspartate aminotransferase levels, suppressed ROS activity, decreased TNF-α and IL-1β levels, and inhibited hepatocyte apoptosis induced by CIH. TUDCA also inhibited CIH-induced ER stress in the liver, as evidenced by decreased expression of BiP, UPR transducers, and ER proapoptotic proteins. Taken together, the results of this latter study describe a liver-protective effect of TUDCA in CIH model mice, an effect that is mediated, at least in part, by inhibition of ER stress [18].

Another similar animal study reported the mechanism of ER stress in CIH-induced brain damage in rats. In this study, overall cognitive function was decreased in CIH model rats, and BiP expression was increased in rats with hippocampal and prefrontal lesions. These data indicate that CIH induces ER stress in the hippocampus and prefrontal cortex. CIH also induced a time-dependent, progressive increase in p-PERK levels in the hippocampus and prefrontal cortex, and downregulated p-eIF2α, a downstream target of PERK, indicating that the PERK signaling pathway is sensitive to CIH-induced ER stress in the hippocampus and prefrontal cortex. The authors of this study further found that, following CIH, p-IRE1 levels were increased, but there were no increases in spliced XBP-1 or EDEM (ER-associated degradation enhancing α-mannosidase-like protein), a downstream target of XBP-1. In addition, they demonstrated that XBP-1 mRNA splicing, activated via the IRE-1 pathway, was not significantly increased after CIH. However, they did find that ATF4 and CHOP were significantly upregulated over time after CIH, and that levels of p-JNK/JNK, apoptotic signaling kinase 1 (ASK1), and TNF receptor-associated factor 2 (TRAF2) were significantly increased. Furthermore, Sal induced a significant increase in eIF2α phosphorylation, but significantly downregulated CHOP after CIH (CIH + Sal group) compared with the CIH-only group. Sal also significantly reduced the number of apoptotic cells after CIH injury, as revealed by TUNEL staining. Collectively, these observations indicate that Sal inhibits CIH-induced neuronal apoptosis in the hippocampus and prefrontal cortex [19].

A final additional study analyzed the correlation between ER stress and the therapeutic effects of continuous positive airway pressure (CPAP) and weight loss, which are typical treatment methods for obese OSA patients. In this study, obese patients were categorized into three groups, as follows: (1) those who showed good adherence to weight loss and CPAP treatment; (2) those who showed poor adherence to treatments, and (3) those who were obese but did not have OSA. The good-adherence group showed significantly decreased expression of ATF4, CHOP, and endoplasmic reticulum oxidoreductin-1 (ERO-1) mRNAs in their adipose tissue compared with the other groups. On the basis of these results, the authors suggested that effective CPAP therapy improves obesity-associated ER stress markers in obese patients with OSA [20].

Taken together, these observations suggest that CIH—the main pathological mechanism of OSA—induces ER stress that impacts the heart, brain, and liver to increase OSA-related morbidity. Given that the known ER stress inhibitors Sal and TUDCA effectively suppressed the activation process or incidence of ER stress, the use of such agents to manage the process appropriately holds promise as a new therapeutic approach to OSA.

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