World Journal of Otorhinolaryngology

Online Submissions: http://www.wjgnet.com/esps/
wjotorhinolaryngol@wjgnet.com
doi:10.5319/wjo.v3.i3.42

World J Otorhinolaryngol 2013 August 28; 3(3): 42-57
ISSN 2218-6247 (online)

FRONTIER

Cause of idiopathic sudden sensorineural hearing loss: The stress response theory

Masatsugu Masuda, Jin Kanzaki

Masatsugu Masuda, Department of Otolaryngology, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka-shi, Tokyo 181-8611, Japan
Jin Kanzaki, Department of Otolaryngology, International University of Health and Welfare, 13-1 Higashikaiganncho, Atami-shi, Shizuoka 413-0012, Japan
Author contributions: Masuda M designed and wrote this paper; Kanzaki J gave an outline of this paper to Masuda M.
Supported by A grant from the Ministry of Health, Labor and Welfare and a Grant-in-Aid for Young Scientists
Correspondence to: Masatsugu Masuda, MD, PhD, Department of Otolaryngology, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka-shi, Tokyo 181-8611, Japan. masoeur13@mac.com
Telephone: +81-422-425968 Fax: +81-422-425968
Received: April 20, 2013 Revised: June 14, 2013
Accepted: July 23, 2013
Published online: August 28, 2013

Abstract

The stress response theory is a relatively new concept about the cause of idiopathic sudden sensorineural hearing loss (ISHL). A number of possible etiologies have been proposed in the literature, as discussed in this paper, but each proposed etiology has been both supported and refuted in the literature. However, the stress response theory can integrate hypotheses that have been advocated so far. The word "stress" refers to a constellation of physical and psychological stimuli including systemic viral and bacterial illness, systemic inflammatory disorders, and physical, mental or metabolic stress. Numerous studies have demonstrated adverse effects of systemic stress on health. Stress causes changes in the immune system and cytokine network through activation of the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system. Several types of catecholamine and cytokine receptors are in the cochlea cells other than capillary cells, and then they can respond to systemic stressors. However, there are few studies examining how systemic stress is associated with cochlear dysfunction. The stress response theory addresses this question. In the theory, a variety of stressors and risk factors contribute to the onset of ISHL in varying degrees. The lateral wall of the cochlea has very unique responses to systemic stressors. It plays a critical role in causing ISHL. Systemic stressors converge at the lateral wall and trigger pathological activation of nuclear factor κ-light-chain-enhancer of activated B cells, a transcriptional factor known as a stress sensor. This activation enhances local expression of genes associated with immune and inflammatory system, resulting in cochlear dysfunction. We review the original stress response theory advocated by Adams *et al* and the integrative stress response theory that integrates our knowledge about the etiologies of ISHL so far.

Key words: Cause; Idiopathic sudden sensorineural hearing loss; Lateral wall; Nuclear factor κ-light-chain-enhancer of activated B cells; Stress

Core tip: The present review focuses on the following four points. First, it summarizes etiologies proposed in the last decade to confirm what we know about the cause of idiopathic sudden sensorineural hearing loss (ISHL). Second, it reviews how systemic stressors affect the human body and the cochlea. Third, it reviews the characteristics of the lateral wall that show unique responses to systemic stressors. Finally, it reviews a relatively new concept about the cause of ISHL, the stress response theory, which integrates our knowledge of the cause of ISHL.

Masuda M, Kanzaki J. Cause of idiopathic sudden sensorineural hearing loss: The stress response theory. *World J Otorhinolaryngol* 2013; 3(3): 42-57 Available from: URL: http://www.wjgnet.com/2218-6247/full/v3/i3/42.htm DOI: http://dx.doi.org/10.5319/wjo.v3.i3.42

INTRODUCTION

Idiopathic sudden sensorineural hearing loss (ISHL) is a moderately common otologic disorder characterized by new onset of unilateral reversible or irreversible sensorineural hearing loss, which generally develops over minutes or several hours. However, the etiology remains unknown. During the past decade, a number of papers on proposed etiologies have been published, including those on vascular disturbance, viral infection, and immune-mediated mechanisms. Table 1 summarizes papers about the cause of ISHL published during this decade[1-73]. Papers for and against vascular etiologies with analysis of genetic polymorphism are increasing. Yet, there is no conclusive evidence, and many different treatments exist for ISHL[74]. In fact, Nosrati-Zarenoe *et al*[75] reported no significant difference in outcomes between treated and non-treated patients (300 patients in total).

To develop and apply the best treatment for ISHL, we must reveal the pathophysiology. Most papers focus on one cause of the disease, and each proposed etiology has papers that support and refute it, as shown in Table 1. On the other hand, the stress response theory can integrate the various hypotheses proposed up to this point, and can explain the clinical characteristics of ISHL. Originally, the theory was advocated by Merchant *et al*[53] and Adams[76]. They proposed that ISHL might be a result of pathologic activation of nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) in the cochlear lateral wall. NF-κB is activated by various stressors, acting as a "stress sensor". It plays a pivotal role in regulating expression of genes associated with immune system and inflammatory responses. For example, interleukin (IL)-6, tumor necrosis factor-α (TNF-α), inducible nitric oxide (iNOS), and intercellular adhesion molecule 1 (ICAM-1) are NF-κB responsive genes[77]. The authors demonstrated that NF-κB was activated in the unilateral cochlear lateral wall by the systemic stressor, *i.e.*, intraperitoneal bacterial endotoxin lipopolysaccharide (LPS) injection, but not by the local stressor, *i.e.*, intratympanic LPS injection (Figure 1A and D). Then, they speculated that ISHL would be the result of pathologic NF-κB activation responding to the systemic stressor.

In the present review, we describe the association of stress and the onset of ISHL, extending the original concept of the stress response theory. To begin, we will quickly review the influence of the chronic psychosocial and physiological stressors on the human body.

OVERVIEW OF CHRONIC STRESS EFFECTS ON HUMAN BODY

Selye *et al*[78,79] defined stress response as the body's nonspecific response when a human being is subjected to stressors, including psychosocial, physical, and biological stimuli. More than half a century ago, Selye *et al*[80] showed that stress caused damage to organs like the heart and the kidney. In recent years, there is accumulating evidence that chronic stress results in many diseases including dermatitis, depression, cardiovascular disease, osteopenia/osteoporosis, immune suppression, and insulin resistance through the activation of the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS)[81-83].

Briefly, stressors induce release of corticotropin-releasing hormone (CRH) from the hypothalamus, CRH induces adrenocorticotropic hormone (ACTH) release from the anterior pituitary, ACTH induces glucocorticoid (GC) secretion from the adrenal cortex, and GC induces norepinephrine (NEP) and epinephrine (EP) release from the adrenal medulla. Stressors and CRH also activate the locus coeruleus of the brainstem, eliciting an SNS response and resulting in NEP and EP release. Furthermore, chronic psychological stress results in a decrease in the sensitivity of immune cells to GC that normally terminates the inflammatory response, which then increases a variety of disease risks[84].

Possible direct effects of the autonomic nervous system on the cochlea

It is well known that the cardiovascular system is directly regulated by the NEP and EP from the SNS, and acetylcholine from the parasympathetic nervous system. In addition, converging evidence from animal and human studies indicates that there is an association between stress and cardiovascular disease[81]. However, the effect of these systemic stress-induced catecholamines on the cochlea remains unknown.

Several types of adrenergic and muscarinic acetylcholine receptors are located in the cochlea and in the endolymphatic sac, as well as in blood vessels like the spiral modiolar artery (Table 2)[85-94]. Their exact functions and synapse formation with autonomic nerve fibers are not clear. However, the stress-induced circulating EP and NEP increase will relay the SNS activity to the inner ear. Parasympathetic nervous system activity will also affect the inner ear, because the activity can be relayed to the whole body by the circulating acetylcholine-synthesizing T cells[95], even if the parasympathetic nerve and the cochlea cells do not have synaptic formation.

Considering that these receptors are on the vessels of the cochlea, the lateral wall, and the endolymphatic sac, they probably contribute to the following functions: (1) regulation of the blood flow; (2) maintenance of the inner ear lymphatic ion homeostasis; and (3) enhancement of the stress response in the lateral wall. We will describe these again later in this review.

Stress-induced dysfunction of immune system through the decrease of natural killer cell activity

Chronic stress disrupts immune system homeostasis and induces susceptibility to infectious and autoimmune diseases[96,97]. Furthermore, there are frequent associations between infectious diseases and autoimmune diseases[98]. The natural killer (NK) cell has critical roles in resistance against both viral and bacterial infections[99,100], and in

Table 1 Proposed causes of idiopathic sudden sensorineural hearing loss during this decade

Main category	Subcategory	Significantly associated factors	NOT significantly associated factor	Ref.
Vascular impairment		MTHFR poly., homocysteine	FV poly., PT poly., AT, LAC, protein S, protein C	[1,2]
	Medical history	MTHFR poly., FV Leiden poly., folate, cardioV risk factors		[3]
	Medical history	Platelet GlyIa poly.	Platelet GlyIIIa poly., Framingham cardioV risk factors, FV Leiden poly., PT poly., history of cardioV events, brain stroke, antiphospholipid syndrome	[4,5]
		PAI-1 poly.		[6]
	Medical history	CFH poly. with DM	HT, lipid	[7]
	Medical history	Low FMD of the brachial artery	Low C-IMTI, LDL, cardioV risk factors	[8]
		Vertebrobasilar junction angulation		[9]
		High global oxidative stress index		[10]
			FV Leiden poly., PT poly.	[11]
	Medical history	SBP, personal/family history cardioV events	FV poly., PT poly., HT, DM, lipid, smoking, personal/family history or in the presence of thrombotic factors	[12]
		PKCH poly., MTHFR poly.		[13,14]
		Cho, LDL		[15]
		Cho, LDL, unsaturated fatty acid, coenzyme Q10, folate, homocysteine	MTHFR poly., FV poly., PT poly., antithrombin Ⅲ, protein C and S, D-dimer, FG, activated protein C resistance	[16-18]
		MTHFR poly., FV Leiden poly., PT poly., platelet GlyIIIaA1/A2 poly., homocysteine, Cho, FG, folate		[19,20]
		MTHFR poly.	FV, PT, EPCR, PAI-1	[21]
	Medical history	ICAM-1, VCAM-1	Cho, triglyceride, FG, ESR, smoking, DM	[22]
		MTHFR poly. with MTR poly., MTR poly.	MTHFR poly. alone	[23]
		FV Leiden poly.	PT poly.	[24]
	Auto-immunity	Cho, homocysteine, PAI-1, anticardiolipin antibodies	FV Leiden poly., FII poly., antithrombin, protein C and S, lupus anticoagulant, lipoprotein(a)	[25]
		eNOS poly.		[26]
		FMD		[27]
		Whole blood viscosity, erythrocyte deformability index, activated clotting time, clot rate, PAI-1 antigen, factor Ⅷ:C	Plasma viscosity, FG	[28]
	Auto-immunity	Antiendothelial cell antibody		[29,30]
Cytokine		IL-1B poly., TNF-β poly.		[31,32]
		TNF-α	IL-10, IL-12	[33]
		IL-6 poly.	IL-4R poly., IL-10 poly., TNF-α poly., TNFRSF1B poly., VEGF poly.	[34]
		IL-1A poly.	IL-1B poly.	[35]
	Vascular impairment		IL-6, IL-8, ICAM-1, VCAM-1, E-selectin, MCP-1, lipid, FG	[36]
		TNF-α, sCD40, sCD40L, T lymphocyte, CD40, cyclooxygenase 2, CD38 positive T or B lymphocyte	Monocyte, macrophage	[37]
Cellular stress		HSP70 poly.		[38]
			GPX1 poli., PON1 poli., PON2 poli., SOD2 poli.	[39]
			GST poly., CYP poly.	[40]
	Auto-immunity		Anti-HSP70 antibody, TNF-α, ESR, ANA, antiphospholipid antibody	[41]
	Auto-immunity	Anti-HSP70 antibody, anti-phospholipids antibody		[42]
		HSP70		[43]
			GST poly.	[44]
Infection		IgA to HSV1	IgG and IgM to CMV, VZV, HSV1, and HSV2. IgA to CMV, VZV, and HSV2	[45]
			Borrelia	[46]
			Herpes zoster	[47]
		Recent subclinical viral infection (cytomegalovirus, herpes simplex, Epstein-Barr virus), toxoplasmosis infections		[48]
			Enterovirus, cytomegalovirus, Epstein-Barr virus	[49]
Auto-immunity			Anti-double stranded DNA, RF, antiphospholipid IgG and M, antinuclear antibody, complements C3 and C4	[50]
		T cell responding to cochlin		[51]
Stress response theory		Neutrophil, NKCA, IL-6	TNF, hCRP	[52]
		Histological evidence of severe osmotic stress of the organ of Corti		[53]

Medical history		HIV		[54]
	Vascular impairment	SLE		[55]
	Vascular impairment	AMI		[56]
		Migrane with HT		[57]
	Vascular impairment	ED		[58]
	Vascular impairment	DM		[59]
		Chronic kidney disease with and without DM		[60]
		Allergy		[61]
		Male with OSA	Female with OSA	[62]
	Vascular impairment	CardioV risk factors, DM, Cho		[63]
		Family history of ISHL		[64]
	Vascular impairment	CerebroV stroke		[65]
Other aetiologies			Aquaporin 4 and 5 poly., estrogen receptor α poly.	[66]
		Round window membrane rupture		[67]
		Endolymphatic hydrops		[68]
			Eustachian tube dysfunction	[69]
		General anaesthesia		[70]
			Month, weather	[71]
		HLA-DQB1 and -DRB1		[72]
			Season, weather	[73]

Papers on human studies are categorized by the proposed etiologies. Papers that deduce possible etiologies from the effect of a treatment are excluded. For example, Kang *et al*[174] stated that the cause might be reactive oxygen metabolites produced by inner ear ischemia or inflammation, because high dose vitamin C was effective. Such papers are excluded from this table in order to save space, although they are noteworthy. AMI: Acute myocardial infarction; AT: Antithrombin; C-IMT: Carotid intima-media thickness; CardioV: Cardio vascular; CDL: CD ligand; CerebroV: Cerebrovascular; CFH: Complement factor H; Cho: Cholesterol; CMV: Cytomegalovirus; CYP: Cytochrome P450; DM: Diabetes mellitus; E-selectin: Endothelial selectin; ED: Erectile dysfunction; eNOS: Endothelial nitric oxide synthase; EPCR: Endothelial cell protein C receptor; ESR: Erythrocyte sedimentation rate; FG: Fibrinogen; FMD: Flow-mediated dilatation; FII: Factor II; FV: Factor V; Gly: Glycoprotein; GPX: Glutathione peroxidase; GST: Glutathione S-transferases; hCRP: High sensitivity C-reactive protein; HIV: Human immunodeficiency virus; HLA: Human leukocyte antigen; HSP: Heat shock protein; HSV: Herpes simplex virus; HT: Hypertension; ICAM-1: Intercellular adhesion molecule 1; IL: Interleukin; ISHL: Idiopathic sudden sensorineural hearing loss; LAC: Lupus anticoagulant; LDL: Low density lipoprotein; MCP-1: Monocyte chemoattractant protein 1; MTHFR: Methylene tetrahydrofolate reductase; MTR: Methionine synthase; NKCA: Natural killer cell activity; OSA: Obstructive sleep apnea; PAI-1: Plasminogen activator inhibitor-1; PKCH: Protein kinase C-Eta; poly.: Polymorphism; PON: Paraoxonase; PT: Prothrombin; RF: Rheumatoid factor; SBP: Systolic blood pressure; SLE: Systemic lupus erythematosus; sCD: Soluble cluster of differentiation; SOD: Superoxide dismutase; TNF: Tumor necrosis factor; TNFRSF1B: Tumor necrosis factor receptor superfamily 1b; VCAM-1: Vascular cell adhesion molecule 1; VEGF: Vascular endothelial growth factor; VZV: Varicella-zoster virus.

Table 2 Receptors of catecholamine in the cochlea

Location	Adrenergic receptor					Cholinergic receptor			
	α1	α2	β1	β2	[1]β	M1	M2	M3	M5
IHC	○		○			○		○	○
OHC	○		○			○		○	
Deiters' cells			○	○		○	○	○	○
Hensen's cells			○	○					
Outer sulcus			○						
Stria vascularis[2]				○					
Strial marginal cell			○						○
Capillaries in the stria vascularis								○	
Spiral ligament[2]			○	○		○	○	○	○
Rissener's membrane					○				
Spiral ganglion	○		○	○		○		○	○
Nerve fibers approaching HCs	○		○	○					
Efferent fibers of the intraganglionic spiral bundle							○		○
Spiral modiolar artery	○	○							
Endolymphatic sac				○					

[1]The specific receptor subtype, β1 or β2, was not determined; [2]Note that the receptors were detected in tissues apart from blood vessels. IHC: Inner hair cell; OHC: Outer hair cell.

regulating autoimmunity[101]. However, NK cell activity (NKCA) is reduced by chronic stress like fatigue, stressful life events, inability to cope with stress, and shortness of sleep[102-106]. Therefore, such chronic stress has the potential to put the host in danger of infectious and autoimmune disease.

Association of stress and cytokines

IL-1, IL-6, and TNF are well known pro-inflammatory cytokines. They are pleiotropic and work as both effectors and regulators of stress response composed of the HPA axis and the SNS[107-109]. Nitric oxide (NO) is also involved in the HPA axix response[110].

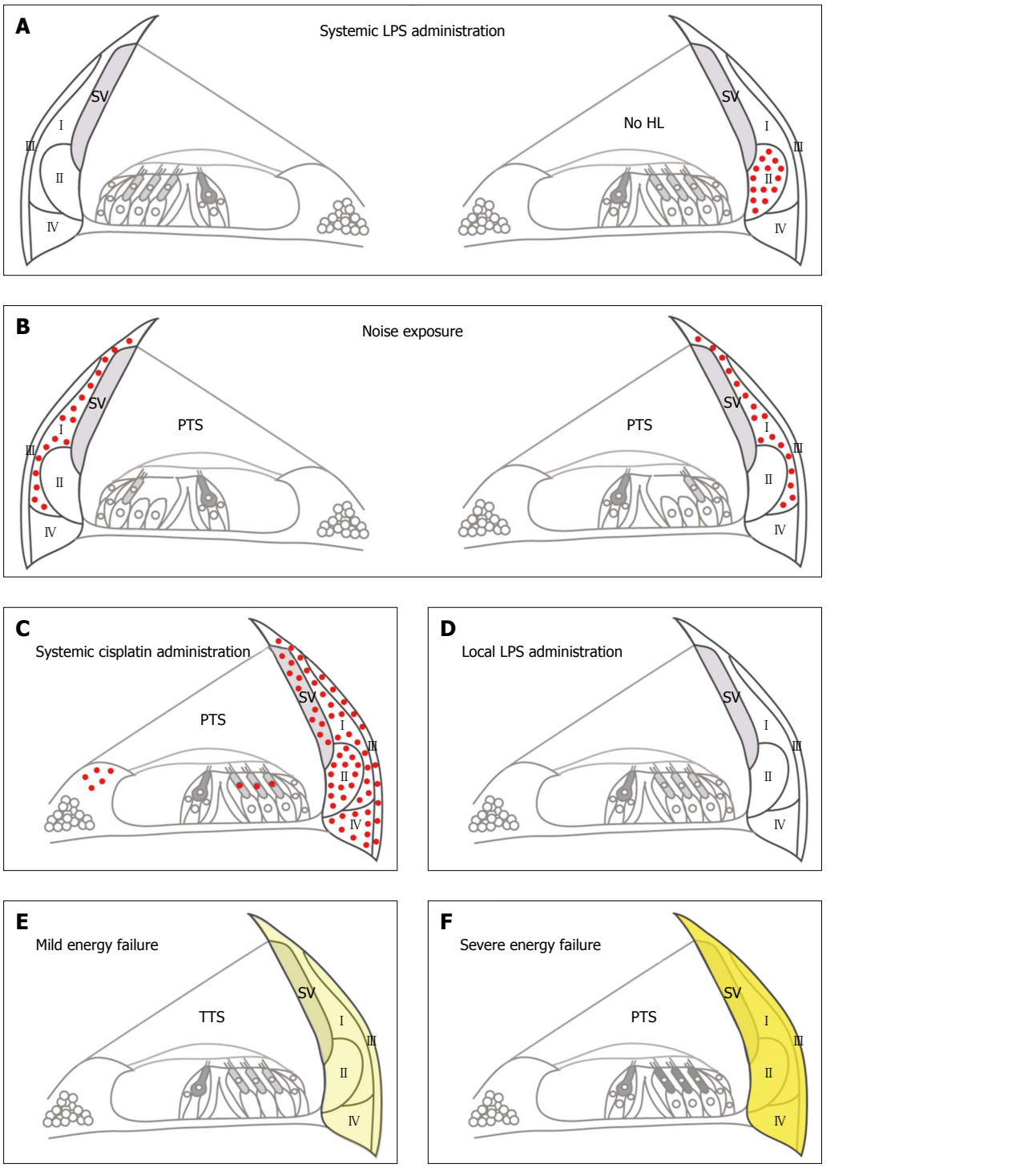

Figure 1 Characteristics of the lateral wall stress response. A-D: The lateral wall is composed of the stria vascularis (SV) and the spiral ligament, in which there are four types of fibrocytes (Ⅰ-Ⅳ). Intraperitoneal lipopolysaccharide (LPS) injection mainly activates nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) (red dots) in the type Ⅱ fibrocytes asymmetrically between the two ears. However, local LPS injection (*i.e.*, intratympanic injection) does not induce the activation. Noise exposure activates NF-κB in type Ⅰ fibrocytes symmetrically at first. Systemic cisplatin injection activates NF-κB in the whole lateral wall, outer hair cells (HCs), and the spiral limbus, and causes HC loss; E: Mild energy failure of the lateral wall causes transient threshold shift (TTS); F: However, severe energy failure causes permanent threshold shift (PTS) with degeneration of cochlear lateral wall, and mild degeneration of the organ of Corti. HL: Hearing loss.

IL-1 is a potent pro-inflammatory cytokine[111], and is produced centrally and periphery following exposure to immunological and psychological stressors[108]. It directly activates the HPA axis and central nervous system, and can even cause depressive symptoms. IL-1 is also known to induce IL-6 strongly[107].

IL-6 is induced by stress as well as by IL-1. Stress-induced increases in IL-6 are a robust finding, and increases are typically higher in adverse psychological conditions[107]. Work stress is associated with an enhancement of IL-6 production by leukocytes before and after infectious stressor and with a lower capacity of GC to suppress IL-6 production[112].

Local and circulating IL-6 can influence the whole body *via* classical- and trans-signaling, respectively. In classical signaling, IL-6 works in cells that express the membrane-bound IL-6 receptor, but only few cells express it, so this signaling works locally. In trans-signaling, a complex of circulating IL-6 bound to the IL-6 receptor, which occurs naturally or by cleavage from apoptotic neutrophil, can control inflammatory response through binding with glycoprotein (gp130), displayed by all cells[113].

The underlying mechanism of IL-6 increase under stress is associated with activation of NF-κB[114,115]. Cortisol and catecholamines in the HPA axis and the SNS induce and enhance NF-κB activation under psychosocial stress[114,116]. Then, NF-κB induces IL-6 expression. IL-6 is not only a transcriptional target of NF-κB, but also an activator of NF-κB[117,118]. Therefore, a positive feedback loop can be made between the two.

Chronic stress also disturbs the circadian rhythm of serum IL-6 levels. Although serum levels of IL-6 reflect circadian cycle, IL-6 decreases less during the night in individuals experiencing negative mood or fatigue than those experiencing uplift events[119]. Conversely, IL-6 elevation per se generates fatigue, fever, and sleep-related symptoms such as daytime somnolence[107].

Additionally, TNF-α also increases under chronic psychosocial stress[106,120-123]. There is in fact a personality type associated with high TNF-α, distressed personality[124]. It may be a possible reason why final health status is different among individuals under the same stress.

NO is generally identified as a molecule involved in neurotransmission, neuromodulation, controlling arterial diameter, and protecting blood vessels from deleterious consequences of platelet aggregation and activation of inflammatory responses[125,126]. It is also involved in the LPS-induced HPA axis response under basal conditions and during its adaptation to chronic social stress circumstances[110]. Excess NO induced by increased iNOS expression leads to the formation of a powerful oxidant, peroxynitrite. It results in cell death by many mechanisms, including lipid peroxidation, protein nitration, DNA damage, or the irreversible inhibition of respiration[127].

The description above concerns the stress response of the whole body. Next, we will review the characteristics of the lateral wall that play a leading role in the stress response theory.

CHARACTERISTICS OF THE COCHLEAR LATERAL WALL

An essential role for cochlear homeostasis

The lateral wall consists of the stria vascularis and the spiral ligament, in which there are four types of fibrocytes (Figure 1). The fibrocytes are classified based on general location, and localization of sodium-potassium-adenosine- triphosphatase (Na^+/K^+-ATPase) and the gap junction protein connexin 26[128-131]. They have a critical role in the potassium ion recycling mechanism[132], and could also be implicated in the mechanisms of glucose transport in the cochlea[133]. Type Ⅲ fibrocytes have even contractility and regulate tension of the basilar membrane, thereby determining auditory sensitivity[134].

In the stria vascularis, there are three types of cells that express multiple ion-transport apparatuses[135]. Therefore, the lateral wall is essential for maintaining cochlear homeostasis, and thus for normal hearing[128,135]. Degeneration of the lateral wall may be implicated in the survival of sensory cells[136].

Association between the extent of lateral wall dysfunction and the degree of hearing loss

Hoya *et al*[137], Mizutari *et al*[138] and Okamoto *et al*[139] demonstrated that different degrees of acute energy failure in the cochlear lateral wall cause different degrees of degeneration of the lateral wall fibrocytes, resulting in different degrees of hearing loss (Figure 1E and F). They administered the mitochondrial toxin 3-nitropropionic acid (3-NP) in the rat cochlea through the round window. Five hundred mmol/L 3-NP caused a permanent threshold shift of more than 80 dB at 8-20 kHz 3 h after 3-NP administration[139]. Marked degeneration of type Ⅱ fibrocytes, type Ⅳ fibrocytes, and cells in the stria vascularis were detected at the same time. Lateral wall degeneration was progressive for at least 14 d. In the organ of Corti, mitochondrial translocation in outer hair cells and mild degeneration of Deiters cells were observed 7 and 14 d after the administration, respectively.

On the other hand, 300 mmol/L 3-NP caused a completely reversible threshold shift at 8 kHz and degeneration of the lateral wall was not observed 3 wk after the 300 mmol/L 3-NP administration[138]. These suggest that mild energy failure of the lateral wall causes temporal and mild disturbance of cochlear homeostasis and temporal hearing loss without loss of inner ear cells. However, severe energy failure causes loss of the lateral wall cells, and then induces structural changes in the organ of Corti resulting in permanent hearing loss.

Wang *et al*[140] demonstrated that different intensities of an octave band noise (8-16 kHz) resulted in degeneration of different kinds of fibrocytes in the lateral wall and different degrees of hearing loss. In the lateral wall, 94 dB SPL noise caused loss of type Ⅳ fibrocytes alone, and resulted in only about 10 dB threshold shift at most. However, more than 112 dB SPL noise caused loss of type Ⅰ, Ⅱ, and Ⅳ fibrocytes, and resulted in more than 60 dB threshold shift.

These findings suggest that degree of the energy failure and the extent of the dysfunctional region in the lateral wall are the critical indicators of the degree of acute hearing loss.

Change of a region where NF-κB is activated in the lateral wall

NF-κB is activated in the lateral wall 24 h or earlier after loading stressors (Table 3)[141-146]. Interestingly, the region where NF-κB is activated changes in the lateral wall depending on the kind of stressor, the degree of the stress

Table 3 Nuclear factor κ-light-chain-enhancer of activated B cells activation and associated cytokine expression in the lateral wall

Animal	Stressor	Time point	NF-κB		Other factors			Ref.
			Response	Location	Factor	Response	Location	
CBA/CaJ mice	LPS, *ip*	24 h	Activation	Unilateral, Ⅱ >> Ⅰ, Lim.				[141]
	LPS, *ip* + dexamethasone, *ip*		No activation					
	Anti-CD3, *ip*		Activation	Ⅰ				
	Taxol, *ip*		Activation	Ⅰ				
	100 dB SPL		Activation	Bilateral, Ⅰ >> Ⅱ, Lim.				
CBA mice	117 dB SPL	4 h	Transcription	LW				[142]
		2-12 h[1] (4 h)			iNOS	Transcription	LW	
		0-12 h (6 h)			ICAM-1	Transcription	LW	
		2-12 h (6 h)			VCAM-1	Transcription	LW	
		14 h			ICAM-1	Expression	SV	
		14 h			VCAM-1	Expression	SV	
Swiss-Webster mice	Ag	7 d			Leukocytes	Expression[2]	SL[3]	[143]
	90 or 100 dB SPL	7 d				No expression		
	90 or 100 dB SPL + Ag	7 d				No expression		
	118 dB SPL	4 h	Activation	Ⅰ, Ⅱ, Ⅳ				
		7 d	No activation		Leukocytes	Expression[2]	LW	
					ICAM-1	Expression	Ⅱ	
	118 dB SPL + Ag	4 h	Activation	Ⅰ, Ⅱ, Ⅳ, HC, SC				
		7 d	Activation	HC, SC	Leukocytes	Expression	LW[4]	
			Activation		ICAM-1	Expression	Ⅱ, Ⅲ >> Ⅰ[4]	
C57/Bl6J mice	124 dB SPL	2 h	Activation	Ⅰ, Ⅱ, Ⅲ, Ⅳ, SV	iNOS	Most of NF-κB activated cells		[144]
		72 h	Activation	Ⅰ, Ⅱ, Ⅲ, Ⅳ, SV[5]	iNOS	Most of NF-κB activated cells[5]		
Sprague-Dawley rats	Cisplatin, *ip*	24 h	Activation	Ⅰ, Ⅱ, Ⅲ, Ⅳ, SV, OHC, Lim.	IL-1β	Expression	Ⅱ, Ⅳ >> Ⅰ, Ⅲ, SMV	[145]
					IL-6	Expression	SMV	
					TNF-α	Expression	Ⅰ, Ⅱ, Ⅲ, Ⅳ, SV, Lim., SMV, HC	
	Cisplatin + TNF-α inhibitor		No activation		IL-1β	No expression, no transcription		
					IL-6	No expression, no transcription		
					TNF-α	No expression, no transcription		
Sprague-Dawley rats	124 dB SPL	3 h			IL-6	Expression	Ⅲ, Ⅳ	[146]
		6 h				Expression	Ⅰ, Ⅱ, Ⅲ, Ⅳ	
		12 h				Expression	Ⅰ, Ⅱ, Ⅲ, Ⅳ, SV, SG	
		24 h				Expression	Ⅰ, Ⅱ, Ⅲ, Ⅳ, SG[6]	

[1]The time in the parentheses is the time of the maximum up-regulation of a factor; [2]The paper did not show whether it was significant or not in only the lateral wall, although it was significant in the total number of leukocytes in the modiolus, spiral limbus (Lim.), spiral ligament (SL), stria vascularis (SV), and the scala tympani. However, the number in the lateral wall showed a clear tendency of increase compared with controls; [3]There were a small number of leukocytes in the spiral ligament; [4]The leukocyte number and the intercellular adhesion molecule 1 (ICAM-1) expression intensity were significantly more than those of Ag alone and 118 dB noise alone in the total of modiolus, Lim., SL, SV, and the scala tympani; [5]The intensity at 72 h was weaker than at 2 h; [6]The intensity at 24 h was much weaker than at 12 h in the lateral wall. Some papers demonstrated nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) activation in the lateral wall and cytokine expression. The systemic stressors that induce stress response of the lateral wall are shown in the column "Stressor". Each paper used different methods and time points to observe the response. For example, the activation of NF-κB (Activation) (*i.e.*, translocation of NF-κB from the cytoplasm into the nucleus), its transcriptional up-regulation (Transcription), and the protein expression (Expression) were analyzed. Some papers demonstrated which types of cells responded to stressors in the lateral wall, but some did not. Noise was band noise for 2 h in all experiments, and the intensities are shown in the table. Ⅰ-Ⅳ, type Ⅰ-Ⅳ fibrocytes in the lateral wall; Ⅱ >> Ⅰ, The NF-κB activation was much stronger in type Ⅱ fibrocytes than type Ⅰ fibrocytes; Ag, An adaptive inner ear immune response was created by sensitizing mice to the keyhole limpet hemocyanin. Then, the mice were sensitized systemically to the antigen in experimental conditions shown as Ag or + Ag in the table. iNOS: Inducible nitric oxide synthase; *ip*: Intraperitoneal injection; LPS: Lipopolysaccharide; LW: The transcriptional up-regulation or the protein expression was observed in the lateral wall: but the specific cell type was not determined; SC: Supporting cell; SMV: Spiral modiolar vein; VCAM-1: Vascular cell adhesion molecule 1; IL: Interleukin; TNF-α: Tumor necrosis factor α; HC: Hair cell; OHC: Outer hair cell.

intensity, and/or the genetic background of animal.

Adams *et al*[141] demonstrated that NF-κB of type I fibrocytes was mainly activated by an octave-band noise (90-112 dB SPL) exposure using CBA/J (Figure 1B). Masuda *et al*[144] applied noise more than two orders of magnitude greater (124 dB SPL), and demonstrated that NF-κB of the whole lateral wall was activated using C57/Bl6J mice. Miyao *et al*[143] demonstrated that NF-κB of

type Ⅰ, Ⅱ, and Ⅳ fibrocytes was activated by octave-band noise (118 dB SPL) exposure using Swiss-Webster mice. These results suggest that the same kind of stressor at different intensities or with different genetic backgrounds activates NF-κB of different regions in the lateral wall.

Different kinds of stressors also cause the different regional activation of NF-κB. As mentioned above, noise first induces NF-κB activation of type Ⅰ fibrocytes in the CBA/Bl6J mice. However, systemic inflammatory stress by peritoneal injection of LPS, a Gram-negative bacterial component, induces the activation in type Ⅱ fibrocytes with little activation in type Ⅰ fibrocytes in mice of the same genetic background (Figure 1A)[76,141]. Systemic TNF secretion by intraperitoneal anti-CD3 or taxol injection induces the same NF-κB activation as that by LPS[141]. In another report, intraperitoneal administration of cisplatin induces NF-κB activation in the whole lateral wall (Figure 1C), and this activation was inhibited by TNF-α inhibitor[145]. These suggest that LPS and cisplatin induces NF-κB activation through TNF and/or other factors that remain to be determined.

Prompt and more intense NF-κB activation in the lateral wall responding to multiple stressors than a single stressor

NF-κB activation in the lateral wall is quick after loading a stressor. For example, activation was confirmed 2 h after noise exposure in the whole lateral wall of C57/Bl6J mice, and less but still significant activation was observed after 72 h (Table 3)[144]. Using Swiss-Webster mice, the activation was observed 4 h after noise exposure but not 7 d after[142]. With intraperitoneal LPS, taxol, or anti-CD3 injection, it was observed in the type Ⅰ fibrocytes of CBA/CaJ mice after 24 h[141].

The promptly activated NF-κB regulates expression of several inflammatory factors like IL-1β, IL-6, TNF-α, iNOS, ICAM-1, and vascular cell adhesion molecule 1 (VCAM-1). IL-1β, IL-6, and TNF-α are pro-inflammatory cytokines and they are effectors and regulators of the HPA axis and the SNS, and excess NO induced by iNOS increase results in cell death, as discussed previously. ICAM-1 and VCAM-1 are critical in mediating adhesion of leukocytes to vascular endothelial cells and transendothelial migration in a variety of acute and chronic inflammatory diseases[147,148]. They also play an essential role in regulating microvascular permeability[149].

It is noteworthy that multiple stressors enhance and prolong the NF-κB activation and the target gene expression, as compared with a single stressor. Miyao *et al*[143] demonstrated that noise-exposure plus intrathecal antigen injection induced longer NF-κB activation, much more intense and wider regional ICAM-1 expression, and more leukocytes induction in the lateral wall than noise-exposure alone or antigen injection alone. The NF-κB activation was observed 4 h after but not 7 d after noise-exposure alone. On the other hand, with noise-exposure plus antigen challenge, the activation was observed even 7 d after.

STRESS RESPONSE THEORY

The original stress response theory of ISHL

There is an anecdotal hypothesis about the onset of ISHL, in which so-called "stress" (*i.e.,* psychological and physical stressors) may be associated with the onset of ISHL. It is reported that fatigue, stressful life events, inability to cope with stress, and shortness of sleep are involved in the onset of ISHL[150-152]. However, this hypothesis has a contradictory survey, as the other hypotheses do (Table 1 and see Merchant *et al*[153]). According to a survey by Japanese Ministry of Health, Labor and Welfare in 1975, rates of ISHL patients complaining of psychological and physical stress were unexpectedly low, 13.7% and 22.5%, respectively. This may suggest that a subjective scale of stress is different among individuals and it is difficult to analyze individual stress just by questionnaires.

Concerning the viral hypothesis, many reports could not show histopathological and biomolecular evidences of viral invasion or infection of the inner ear. With respect to the vascular hypothesis, it alone is not enough to explain the clinical characteristics of ISHL. For example, ISHL is not necessarily more prevalent in the elderly, does not accompany other vascular disease, and does not generally recur, making it very different from the cerebral ischemia. Furthermore, only two of 29 ears with ISHL examined showed histopathological evidence of vascular insult to the cochlea, consisting of deposition of connective tissue and new bone within the cochlea.

Finally, Merchant *et al*[53] and Adams *et al*[76,141] proposed that the stress response of the lateral wall to systemic stress is the cause of ISHL. They observed the inner ear of a patient who died 9 d after the onset of ISHL. In the affected cochlea, the organ of Corti showed marked swelling with edema, vacuole formation within the cytoplasm, and blurring of cell boundaries. They interpreted this as evidence that the cells in the organ of Corti were under severe osmotic stress, which must have resulted from lymphatic homeostasis disruption in the cochlea. In their paper published in 2005, they speculated that osmotic stress-induced NF-κB activation within the supporting cells may be an important mechanism causing ISHL in addition to the activation in the lateral wall[53]. However, using a sophisticated animal model in 2009, they demonstrated that cells of the organ of Corti and spiral ganglion were remarkable for the lack of NF-κB activation by systemic inflammatory stress[141]. On the other hand, type Ⅱ fibrocytes in the lateral wall predominantly showed the activation. The lateral wall plays an essential role in maintaining the cochlear homeostasis. In addition, NF-κB is a well-known transcription factor that directly leads to inflammatory cytokine production, and it was observed in animal and human lateral walls, but not in the organ of Corti. Conclusively, the original hypothesis by Adams *et al*[141] is that ISHL is the result of the stress response of the cochlear lateral wall through NF-κB activation responding to the systemic stress and dysfunction of the lateral wall, and

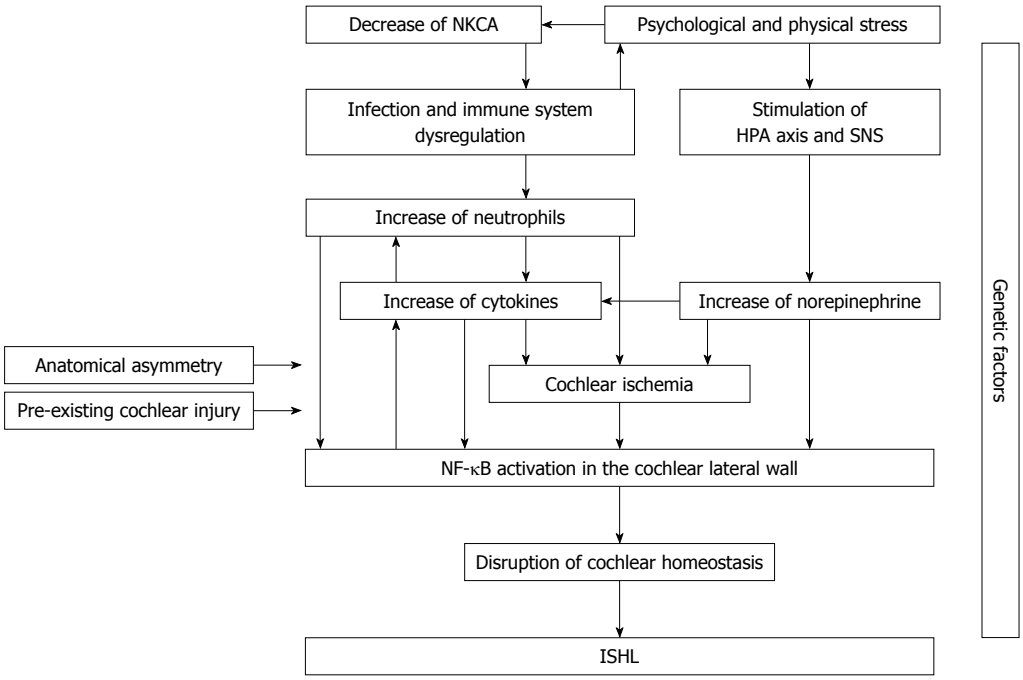

Figure 2 The stress response theory. Synchronism of different types of stressors activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) of the cochlear lateral wall and cause idiopathic sudden sensorineural hearing loss (ISHL). The causative factors should occur in order to make an effective positive feedback loop for breaking open the abnormal NF-κB activation in the lateral wall. Stressful life-events decrease natural killer cell activity (NKCA), stimulate the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), and increase cytokines. The decrease of NKCA induces subclinical infection and/or immune system dysregulation, and then neutrophils and cytokines increase acutely, making the positive feedback loop. The acute increase of neutrophils and a cytokine like tumor necrosis factor alpha impede blood flow, resulting in acute energy failure of the lateral wall. Systemic stressors also induce and enhance norepinephrine-dependent NF-κB activation and cytokine production through the HPA axis and the SNS. They trigger the lateral wall NF-κB activation. Anatomical asymmetry, pre-existing cochlear injury, and innate factors should be involved in the flow considering the clinical characteristics of ISHL. These factors potentially explain why ISHL usually affects the ear unilaterally, why prevalence is much lower in childhood than in adulthood, and why ISHL does not affect all persons under stress. Modified from[52].

the changes of the organ of Corti cells are the secondary phenomenon to the lateral wall dysfunction.

They demonstrated that intraperitoneal LPS injection, *i.e.,* systemic stress, consistently resulted in NF-κB activation in the lateral wall unilaterally but not bilaterally, and the intratympanic LPS injection, *i.e.,* local stress, did not induce the lateral wall NF-κB activation of the mouse cochlea (Figure 1A and D). This seems to reflect the clinical characteristics of the onset of ISHL: acute onset is consistent with the prompt activation profile of NF-κB, most of cases with ISHL are unilateral, and it is not accompanied with the middle ear inflammation. They speculated that systemic cytokines like TNF-α induced by intraperitoneal LPS injection activate the lateral wall NF-κB.

However, intraperitoneal LPS injection alone activates NF-κB in the type Ⅱ fibrocytes alone and did not cause hearing loss in mice[141]. Additionally, intraperitoneal injection of anti-CD3 and taxol, which are known to induce TNF secretion, activate NF-κB in the type Ⅱ cells alone. These observations shed light on the two points: (1) a wider range of NF-κB activation in the lateral wall is needed to cause hearing loss; and (2) systemic stress by infection followed by cytokine increase alone is not enough to induce such a wide range of NF-κB activation. Therefore, the synergistic effect of multiple stressors must be necessary to induce the wide range of lateral wall NF-κB activation resulting in hearing loss.

Next, we will discuss and review how a variety of stressors including psychological and physical stressors converge in lateral wall NF-κB activation and cause ISHL.

The integrative stress response theory of ISHL

We have reviewed how psychosocial and physical stress affect the HPA axis, the SNS, the immune system, inflammatory factors, and a cytokine network. These systemic stress responses can synergistically induce and enhance lateral wall NF-κB activation (Figure 2). Although it is still impossible to demonstrate the live NF-κB activation in the human cochlea, Masuda *et al*[52] recently found evidence for the stress response theory using ISHL patients' blood sample analysis.

So-called "stress," as in chronic psychosocial and physical stress, results in EP and NEP increases through the HPA axis and SNS activation, and the cochlear lateral wall expresses these receptors (Table 2). Therefore, the stress-induced catecholamines can induce and enhance NEP-dependent NF-κB activation. Therefore, the stress-induced catecholamines can induce and enhance NEP-dependent NF-κB activation[114,154], and induce the target gene expression including pro-inflammatory cytokine, adhesion molecules, and iNOS (Table 3).

Stress decreases NKCA, resulting in dysregulation of the immune system and subclinical infections. This immune system disturbance is involved in the stress response

theory. In fact, some authors have suggested that subclinical infection is associated with onset in some ISHL patients after detecting the elevated erythrocyte sedimentation rate or specific antibodies against viruses[45,48,155].

Infection also enhances immune system dysregulation, cytokine production, and psychological stress[156]. Note that bacteria and virus do not attack the inner ear directly in the "infection" we describe here, but they change the whole immune system and have influence on the inner ear homeostasis afterward. These will lead to an increase of circulating neutrophil and cytokines like IL-6; there is a positive feedback loop between neutrophil and IL-6[157-159]. Stress also results in an abnormal immune state. Furthermore, the neutrophil increase induces cochlear energy shortage by impeding the blood flow, because neutrophils have a thrombogenic profile and are known to have association with the risk and prognosis of myocardial infarction and stroke[160-162]. Such an energy shortage induces stress response of the cochlear lateral wall.

Increase of circulating cytokines can also activate lateral wall NF-κB. IL-6 is a target and a regulator of NF-κB, and can have an impact on the NF-κB activation through classic and trans-signaling because the IL-6 receptor and gp130 are expressed in the lateral wall[163]. Circulating TNF-α activates NF-κB of the lateral wall. It also enhances microvascular tone and reduces blood flow in the cochlea[164], resulting in the lateral wall energy shortage.

The whole systemic stressors mentioned above converge synergistically to the NF-κB activation in the lateral wall. The NF-κB activation initiates inflammatory responses in the lateral wall locally. The NF-κB-induced inflammatory cytokines will affect the lateral wall cell function that maintains cochlear homeostasis. The cytokines will also exacerbate inflammatory responses of the lateral wall through enhancing vascular permeability and recruitment of leukocytes[165,166], because the blood supply to the lateral wall is abundant. In rabbits, for example, the lateral wall contains more than 80% of total cochlear blood[167]. The disruption of cochlear homeostasis ultimately causes ISHL. In fact, an ISHL-affected ear has high concentration of proteins in the inner ear fluid space using fluid-attenuated inversion recovery MRI[168-170], suggesting the disruption of cochlear homeostasis.

To explain clinical characteristics of ISHL, the integrative stress response theory should be integrated with other possible factors. At first, ISHL usually affects the unilateral ear, and the prevalence is much lower in childhood than in adulthood. Minor pre-existing subclinical damage in the inner ear or asymmetry of terminal vascular structure (for example, stenotic or not stenotic, straight or torturous) could be a potential explanation for the clinical characteristics of ISHL.

All persons under stress do not suffer from ISHL. Therefore, there must be innate factors for ISHL onset, probably including polymorphisms of genes encoding coagulation factors, vascular tone, and cytokines, among others (Table 1). Even individual personality is likely be involved in differential stress response.

Summary of the stress response theory

A quest for a single definitive cause of ISHL does not seem to be reasonable after reviewing the literature. The basic and critical concept of the stress response theory is that ISHL must not result from a specific single and local cause in the inner ear. Moreover, ISHL should encompass several causes contributing to different degrees of severity and prognosis. Synchronism of different types of factors and different degrees of contribution of each factor could result in the individual ISHL case. Some of these factors must occur rarely, and each factor must occur in a temporally appropriate order to trigger pathological NF-κB activation in the cochlear lateral wall. Therefore, ISHL does not recur frequently, even in the same individual.

Future studies about ISHL in terms of the stress response theory

We have described the possibility that psychosocial and physical stress increase the likelihood of disruption of cochlear homeostasis. Long-term stress should be detected objectively, as in HbA1c for analyzing blood sugar level over periods of 1 or 2 mo in diabetic patients. Monocyte chemotactic protein-1, epidermal growth factor, and vascular endothelial growth factor have been expected to be prolonged psychosocial stress markers[171], but the validity is still controversial[172]. There are controversies about the association of pro-inflammatory cytokines and ISHL as well[31-36,41,52] (Table 1). It may not be enough to measure and analyze the value of each biomarker separately. A new method that analyzes a complicated network consisting of multiple factors will be needed. Broderick *et al*[173] focused on the network of cytokines in which cytokine-cytokine associations are demonstrated topologically, and they demonstrated that the network of subjects with chronic fatigue syndrome deferred in topology significantly compared with healthy subjects.

Therefore, it is vital to integrate of our knowledge and comprehensive analysis of possible etiologies to reveal the pathophysiology of ISHL.

REFERENCES

1 **Fusconi M**, Chistolini A, Angelosanto N, Pignoloni P, Tombolini M, De Virgilio A, Pagliarella M, de Vincentiis M. Role of genetic and acquired prothrombotic risk factors in genesis of sudden sensorineural hearing loss. *Audiol Neurootol* 2011; **16**: 185-190 [PMID: 20798492 DOI: 10.1159/000319310]

2 **Fusconi M**, Chistolini A, de Virgilio A, Greco A, Massaro F, Turchetta R, Benincasa AT, Tombolini M, de Vincentiis M. Sudden sensorineural hearing loss: a vascular cause? Analysis of prothrombotic risk factors in head and neck. *Int J Audiol* 2012; **51**: 800-805 [PMID: 22928918 DOI: 10.3109/14992027.2012.705904]

3 **Lin RJ**, Krall R, Westerberg BD, Chadha NK, Chau JK. Systematic review and meta-analysis of the risk factors for sudden sensorineural hearing loss in adults. *Laryngoscope* 2012; **122**: 624-635 [PMID: 22252719 DOI: 10.1002/lary.22480]

4 **Ballesteros F**, Alobid I, Tassies D, Reverter JC, Scharf RE, Guilemany JM, Bernal-Sprekelsen M. Is there an overlap between sudden neurosensorial hearing loss and cardiovascular risk factors? *Audiol Neurootol* 2009; **14**: 139-145 [PMID: 19005247 DOI: 10.1159/000171475]

5 **Ballesteros F**, Tassies D, Reverter JC, Alobid I, Bernal-Sprekelsen M. Idiopathic sudden sensorineural hearing loss: classic cardiovascular and new genetic risk factors. *Audiol Neurootol* 2012; **17**: 400-408 [PMID: 22948415 DOI: 10.1159/000341989]

6 **Cho SH**, Chen H, Kim IS, Yokose C, Kang J, Cho D, Cai C, Palma S, Busi M, Martini A, Yoo TJ. Association of the 4 g/5 g polymorphism of plasminogen activator inhibitor-1 gene with sudden sensorineural hearing loss. A case control study. *BMC Ear Nose Throat Disord* 2012; **12**: 5 [PMID: 22672326 DOI: 10.1186/1472-6815-12-5]

7 **Nishio N**, Teranishi M, Uchida Y, Sugiura S, Ando F, Shimokata H, Sone M, Otake H, Kato K, Yoshida T, Tagaya M, Hibi T, Nakashima T. Contribution of complement factor H Y402H polymorphism to sudden sensorineural hearing loss risk and possible interaction with diabetes. *Gene* 2012; **499**: 226-230 [PMID: 22426290 DOI: 10.1016/j.gene.2012.02.027]

8 **Ciccone MM**, Cortese F, Pinto M, Di Teo C, Fornarelli F, Gesualdo M, Mezzina A, Sabatelli E, Scicchitano P, Quaranta N. Endothelial function and cardiovascular risk in patients with idiopathic sudden sensorineural hearing loss. *Atherosclerosis* 2012; **225**: 511-516 [PMID: 23102449 DOI: 10.1016/j.atherosclerosis.2012.10.024]

9 **Kim C**, Sohn JH, Choi HC. Vertebrobasilar angulation and its association with sudden sensorineural hearing loss. *Med Hypotheses* 2012; **79**: 202-203 [PMID: 22688399 DOI: 10.1016/j.mehy.2012.04.035]

10 **Capaccio P**, Pignataro L, Gaini LM, Sigismund PE, Novembrino C, De Giuseppe R, Uva V, Tripodi A, Bamonti F. Unbalanced oxidative status in idiopathic sudden sensorineural hearing loss. *Eur Arch Otorhinolaryngol* 2012; **269**: 449-453 [PMID: 21706323 DOI: 10.1007/s00405-011-1671-2]

11 **Lan MY**, Shiao JY, Hsu YB, Lin FY, Lin JC. A preliminary study on the role of inherited prothrombotic risk factors in Taiwanese patients with sudden sensorineural hearing loss. *Eur Arch Otorhinolaryngol* 2011; **268**: 817-822 [PMID: 21170721 DOI: 10.1007/s00405-010-1457-y]

12 **Mosnier I**, Stepanian A, Baron G, Bodenez C, Robier A, Meyer B, Fraysse B, Bertholon P, Defay F, Ameziane N, Ferrary E, Sterkers O, de Prost D. Cardiovascular and thromboembolic risk factors in idiopathic sudden sensorineural hearing loss: a case-control study. *Audiol Neurootol* 2011; **16**: 55-66 [PMID: 20551629 DOI: 10.1159/000312640]

13 **Uchida Y**, Sugiura S, Ando F, Shimokata H, Nakashima T. Association of the C677T polymorphism in the methylenetetrahydrofolate reductase gene with sudden sensorineural hearing loss. *Laryngoscope* 2010; **120**: 791-795 [PMID: 20213658 DOI: 10.1002/lary.20809]

14 **Uchida Y**, Sugiura S, Nakashima T, Ando F, Shimokata H. Contribution of 1425G/A polymorphism in protein kinase C-Eta (PRKCH) gene and brain white matter lesions to the risk of sudden sensorineural hearing loss in a Japanese nested case-control study. *J Neurogenet* 2011; **25**: 82-87 [PMID: 21756056 DOI: 10.3109/01677063.2011.591462]

15 **Oreskovic Z**, Shejbal D, Bicanic G, Kekic B. Influence of lipoproteins and fibrinogen on pathogenesis of sudden sensorineural hearing loss. *J Laryngol Otol* 2011; **125**: 258-261 [PMID: 21054908 DOI: 10.1017/S0022215110002252]

16 **Cadoni G**, Agostino S, Scipione S, Galli J. Low serum folate levels: a risk factor for sudden sensorineural hearing loss? *Acta Otolaryngol* 2004; **124**: 608-611 [PMID: 15267180]

17 **Cadoni G**, Scipione S, Rocca B, Agostino S, La Greca C, Bonvissuto D, Paludetti G. Lack of association between inherited thrombophilic risk factors and idiopathic sudden sensorineural hearing loss in Italian patients. *Ann Otol Rhinol Laryngol* 2006; **115**: 195-200 [PMID: 16572609]

18 **Cadoni G**, Scorpecci A, Cianfrone F, Giannantonio S, Paludetti G, Lippa S. Serum fatty acids and cardiovascular risk factors in sudden sensorineural hearing loss: a case-control study. *Ann Otol Rhinol Laryngol* 2010; **119**: 82-88 [PMID: 20336917]

19 **Capaccio P**, Cuccarini V, Ottaviani F, Fracchiolla NS, Bossi A, Pignataro L. Prothrombotic gene mutations in patients with sudden sensorineural hearing loss and cardiovascular thrombotic disease. *Ann Otol Rhinol Laryngol* 2009; **118**: 205-210 [PMID: 19374152]

20 **Capaccio P**, Ottaviani F, Cuccarini V, Bottero A, Schindler A, Cesana BM, Censuales S, Pignataro L. Genetic and acquired prothrombotic risk factors and sudden hearing loss. *Laryngoscope* 2007; **117**: 547-551 [PMID: 17334320 DOI: 10.1097/MLG.0b013e31802f3c6a]

21 **Yildiz Z**, Ulu A, Incesulu A, Ozkaptan Y, Akar N. The importance of thrombotic risk factors in the development of idiopathic sudden hearing loss. *Clin Appl Thromb Hemost* 2008; **14**: 356-359 [PMID: 18160602 DOI: 10.1177/1076029607306399]

22 **Quaranta N**, Ramunni A, Brescia P, D'Elia A, Vacca A, Ria R. Soluble intercellular adhesion molecule 1 and soluble vascular cell adhesion molecule 1 in sudden hearing loss. *Otol Neurotol* 2008; **29**: 470-474 [PMID: 18401280 DOI: 10.1097/MAO.0b013e318170b650]

23 **Gross M**, Friedman G, Eliashar R, Koren-Morag N, Goldschmidt N, Atta IA, Ben-Yehuda A. Impact of methionine synthase gene and methylenetetrahydrofolate reductase gene polymorphisms on the risk of sudden sensorineural hearing loss. *Audiol Neurootol* 2006; **11**: 287-293 [PMID: 16778415 DOI: 10.1159/000093957]

24 **Görür K**, Tuncer U, Eskandari G, Ozcan C, Unal M, Ozsahinoglu C. The role of factor V Leiden and prothrombin G20210A mutations in sudden sensorineural hearing loss. *Otol Neurotol* 2005; **26**: 599-601 [PMID: 16015153]

25 **Marcucci R**, Alessandrello Liotta A, Cellai AP, Rogolino A, Berloco P, Leprini E, Pagnini P, Abbate R, Prisco D. Cardiovascular and thrombophilic risk factors for idiopathic sudden sensorineural hearing loss. *J Thromb Haemost* 2005; **3**: 929-934 [PMID: 15869586 DOI: 10.1111/j.1538-7836.2005.01310.x]

26 **Fatini C**, Mannini L, Sticchi E, Cecchi E, Bruschettini A, Leprini E, Pagnini P, Gensini GF, Prisco D, Abbate R. eNOS gene affects red cell deformability: role of T-786C, G894T, and 4a/4b polymorphisms. *Clin Appl Thromb Hemost* 2005; **11**: 481-488 [PMID: 16244776]

27 **Balletshofer BM**, Stock J, Rittig K, Lehn-Stefan A, Braun N, Burkart F, Plontke S, Klingel R, Häring HU. Acute effect of rheopheresis on peripheral endothelial dysfunction in patients suffering from sudden hearing loss. *Ther Apher Dial* 2005; **9**: 385-390 [PMID: 16202012 DOI: 10.1111/j.1744-9987.2005.00316.x]

28 **Mannini L**, Paniccia R, Cecchi E, Alessandrello Liotta A, Leprini E, Berloco P, Pagnini P, Abbate R, Franco Gensini G, Prisco D. Reduced erythrocyte deformability and hypercoagulability in idiopathic sudden sensorineural hearing loss. *Clin Hemorheol Microcirc* 2005; **33**: 47-55 [PMID: 16037632]

29 **Cadoni G**, Agostino S, Manna R, De Santis A, Fetoni AR, Vulpiani P, Ottaviani F. Clinical associations of serum anti-endothelial cell antibodies in patients with sudden sensorineural hearing loss. *Laryngoscope* 2003; **113**: 797-801 [PMID: 12792313 DOI: 10.1097/00005537-200305000-00006]

30 **Cadoni G**, Fetoni AR, Agostino S, De Santis A, Manna R, Ottaviani F, Paludetti G. Autoimmunity in sudden sensorineural hearing loss: possible role of anti-endothelial cell autoantibodies. *Acta Otolaryngol Suppl* 2002; **122**: 30-33 [PMID: 12211354]

31 **Um JY**, Jang CH, Kim HL, Cho YB, Park J, Lee SJ, Kim YB, Kim HJ, Ahn KS, Jang HJ, Lee SG, Lee H, Lee KM, Kim SJ, Hong SH. Proinflammatory cytokine IL-1 β polymorphisms in sudden sensorineural hearing loss. *Immunopharmacol Immunotoxicol* 2013; **35**: 52-56 [PMID: 23013363 DOI: 10.3109/08923973.2012.719523]

32 **Um JY**, Jang CH, Kim KY, Kim SJ, Kim NH, Moon PD, Choi IY, Myung NY, Jeong HJ, Hong SH, Kim HM. Candidate genes of cerebrovascular disease and sudden sensorineural

hearing loss. *Clin Appl Thromb Hemost* 2010; **16**: 559-562 [PMID: 19833626 DOI: 10.1177/1076029609348313]
33 **Demirhan E**, Eskut NP, Zorlu Y, Cukurova I, Tuna G, Kirkali FG. Blood levels of TNF-α, IL-10, and IL-12 in idiopathic sudden sensorineural hearing loss. *Laryngoscope* 2013; **123**: 1778-1781 [PMID: 23382065 DOI: 10.1002/lary.23907]
34 **Hiramatsu M**, Teranishi M, Uchida Y, Nishio N, Suzuki H, Kato K, Otake H, Yoshida T, Tagaya M, Suzuki H, Sone M, Sugiura S, Ando F, Shimokata H, Nakashima T. Polymorphisms in genes involved in inflammatory pathways in patients with sudden sensorineural hearing loss. *J Neurogenet* 2012; **26**: 387-396 [PMID: 22385075 DOI: 10.3109/01677063.2011.652266]
35 **Furuta T**, Teranishi M, Uchida Y, Nishio N, Kato K, Otake H, Yoshida T, Tagaya M, Suzuki H, Sugiura M, Sone M, Hiramatsu M, Sugiura S, Ando F, Shimokata H, Nakashima T. Association of interleukin-1 gene polymorphisms with sudden sensorineural hearing loss and Ménière's disease. *Int J Immunogenet* 2011; **38**: 249-254 [PMID: 21385326 DOI: 10.1111/j.1744-313X.2011.01004.x]
36 **Haubner F**, Martin L, Steffens T, Strutz J, Kleinjung T. The role of soluble adhesion molecules and cytokines in sudden sensorineural hearing loss. *Otolaryngol Head Neck Surg* 2011; **144**: 575-580 [PMID: 21493238 DOI: 10.1177/0194599810394324]
37 **Kassner SS**, Schöttler S, Bonaterra GA, Stern-Sträter J, Sommer U, Hormann K, Kinscherf R, Gössler UR. Proinflammatory and proadhesive activation of lymphocytes and macrophages in sudden sensorineural hearing loss. *Audiol Neurootol* 2011; **16**: 254-262 [PMID: 20980746 DOI: 10.1159/000320610]
38 **Chien CY**, Chang NC, Tai SY, Wang LF, Wu MT, Ho KY. Heat shock protein 70 gene polymorphisms in sudden sensorineural hearing loss. *Audiol Neurootol* 2012; **17**: 381-385 [PMID: 22922572 DOI: 10.1159/000341815]
39 **Teranishi M**, Uchida Y, Nishio N, Kato K, Otake H, Yoshida T, Suzuki H, Sone M, Sugiura S, Ando F, Shimokata H, Nakashima T. Polymorphisms in genes involved in oxidative stress response in patients with sudden sensorineural hearing loss and Ménière's disease in a Japanese population. *DNA Cell Biol* 2012; **31**: 1555-1562 [PMID: 22877234 DOI: 10.1089/dna.2012.1631]
40 **Um JY**, Jang CH, Kim SJ, Kim HL, Kim SY, Cho YB, Hong SH. Steroid combination therapy and detoxification enzyme gene polymorphisms in sudden sensorineural hearing loss patients. *Otol Neurotol* 2011; **32**: 872-876 [PMID: 21389901 DOI: 10.1097/MAO.0b013e31821341ac]
41 **Süslü N**, Yilmaz T, Gürsel B. Utility of anti-HSP 70, TNF-alpha, ESR, antinuclear antibody, and antiphospholipid antibodies in the diagnosis and treatment of sudden sensorineural hearing loss. *Laryngoscope* 2009; **119**: 341-346 [PMID: 19160386 DOI: 10.1002/lary.20050]
42 **Gross M**, Eliashar R, Ben-Yaakov A, Ulmansky R, Elidan J. Prevalence and clinical significance of anticardiolipin, anti-beta2-glycoprotein-1, and anti-heat shock protein-70 autoantibodies in sudden sensorineural hearing loss. *Audiol Neurootol* 2008; **13**: 231-238 [PMID: 18259075 DOI: 10.1159/000115432]
43 **Park SN**, Yeo SW, Park KH. Serum heat shock protein 70 and its correlation with clinical characteristics in patients with sudden sensorineural hearing loss. *Laryngoscope* 2006; **116**: 121-125 [PMID: 16481823 DOI: 10.1097/01.mlg.0000187401.75156.b2]
44 **Cadoni G**, Boccia S, Scipione S, Arzani D, Cianfagna F, Ricciardi G, Paludetti G, Agostino S. Glutathione s-transferase gene polymorphisms in Italian patients with sudden sensorineural hearing loss. *Otol Neurotol* 2006; **27**: 1166-1169 [PMID: 16788422 DOI: 10.1097/01.mao.0000226303.59198.ce]
45 **Scalia G**, Palermo CI, Maiolino L, Costanzo CM, Zappal D, Grillo C, Martines AM, Cocuzza S, Russo R, Serra A. Detection of serum IgA to HSV1 and its diagnostic role in sudden hearing loss. *New Microbiol* 2013; **36**: 41-47 [PMID: 23435814]
46 **Bakker R**, Aarts MC, van der Heijden GJ, Rovers MM. No evidence for the diagnostic value of Borrelia serology in patients with sudden hearing loss. *Otolaryngol Head Neck Surg* 2012; **146**: 539-543 [PMID: 22394551 DOI: 10.1177/0194599811432535]
47 **Sheu JJ**, Keller JJ, Chen YH, Wu CS, Lin HC. No increased risk of sudden sensorineural hearing loss following recent herpes zoster: a nationwide population-based study. *Acta Otolaryngol* 2012; **132**: 167-172 [PMID: 22201558 DOI: 10.3109/00016489.2011.633227]
48 **Kikidis D**, Nikolopoulos TP, Kampessis G, Stamatiou G, Chrysovergis A. Sudden sensorineural hearing loss: subclinical viral and toxoplasmosis infections as aetiology and how they alter the clinical course. *ORL J Otorhinolaryngol Relat Spec* 2011; **73**: 110-115 [PMID: 21389742 DOI: 10.1159/000324210]
49 **Gross M**, Wolf DG, Elidan J, Eliashar R. Enterovirus, cytomegalovirus, and Epstein-Barr virus infection screening in idiopathic sudden sensorineural hearing loss. *Audiol Neurootol* 2007; **12**: 179-182 [PMID: 17259705 DOI: 10.1159/000099021]
50 **Cho CH**, Jung BS, Jung JH, Lee JH, Lee JH. Expression of autoantibodies in patients with sudden sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 2013; **122**: 131-134 [PMID: 23534128]
51 **Baek MJ**, Park HM, Johnson JM, Altuntas CZ, Jane-Wit D, Jaini R, Solares CA, Thomas DM, Ball EJ, Robertson NG, Morton CC, Hughes GB, Tuohy VK. Increased frequencies of cochlin-specific T cells in patients with autoimmune sensorineural hearing loss. *J Immunol* 2006; **177**: 4203-4210 [PMID: 16951386]
52 **Masuda M**, Kanzaki S, Minami S, Kikuchi J, Kanzaki J, Sato H, Ogawa K. Correlations of inflammatory biomarkers with the onset and prognosis of idiopathic sudden sensorineural hearing loss. *Otol Neurotol* 2012; **33**: 1142-1150 [PMID: 22872174 DOI: 10.1097/MAO.0b013e3182635417]
53 **Merchant SN**, Adams JC, Nadol JB. Pathology and pathophysiology of idiopathic sudden sensorineural hearing loss. *Otol Neurotol* 2005; **26**: 151-160 [PMID: 15793397]
54 **Lin C**, Lin SW, Weng SF, Lin YS. Increased risk of sudden sensorineural hearing loss in patients with human immunodeficiency virus aged 18 to 35 years: a population-based cohort study. *JAMA Otolaryngol Head Neck Surg* 2013; **139**: 251-255 [PMID: 23429891 DOI: 10.1001/jamaoto.2013.1709]
55 **Lin C**, Lin SW, Weng SF, Lin YS. Risk of sudden sensorineural hearing loss in patients with systemic lupus erythematosus: a population-based cohort study. *Audiol Neurootol* 2013; **18**: 95-100 [PMID: 23257626 DOI: 10.1159/000345512]
56 **Keller JJ**, Wu CS, Kang JH, Lin HC. Association of acute myocardial infarction with sudden sensorineural hearing loss: a population-based case-control study. *Audiol Neurootol* 2013; **18**: 3-8 [PMID: 22948477 DOI: 10.1159/000341988]
57 **Chu CH**, Liu CJ, Fuh JL, Shiao AS, Chen TJ, Wang SJ. Migraine is a risk factor for sudden sensorineural hearing loss: a nationwide population-based study. *Cephalalgia* 2013; **33**: 80-86 [PMID: 23197354 DOI: 10.1177/0333102412468671]
58 **Keller JJ**, Chen YK, Lin HC. A case-control analysis on the association between erectile dysfunction and sudden sensorineural hearing loss in Taiwan. *J Sex Med* 2012; **9**: 1411-1417 [PMID: 22429794 DOI: 10.1111/j.1743-6109.2012.02669.x]
59 **Lin SW**, Lin YS, Weng SF, Chou CW. Risk of developing sudden sensorineural hearing loss in diabetic patients: a population-based cohort study. *Otol Neurotol* 2012; **33**: 1482-1488 [PMID: 23064384 DOI: 10.1097/MAO.0b013e318271397a]
60 **Lin C**, Hsu HT, Lin YS, Weng SF. Increased risk of getting sudden sensorineural hearing loss in patients with chronic kidney disease: a population-based cohort study. *Laryngoscope* 2013; **123**: 767-773 [PMID: 22927011 DOI: 10.1002/lary.23669]
61 **Keleş E**, Sapmaz E, Gödekmerdan A. The role of allergy in the etiopathogenesis of idiopathic sudden sensorineural hearing loss. *Eur Arch Otorhinolaryngol* 2013; **270**: 1795-1801 [PMID: 23008128 DOI: 10.1007/s00405-012-2189-y]
62 **Sheu JJ**, Wu CS, Lin HC. Association between obstructive sleep apnea and sudden sensorineural hearing loss: a

population-based case-control study. *Arch Otolaryngol Head Neck Surg* 2012; **138**: 55-59 [PMID: 22249630 DOI: 10.1001/archoto.2011.227]
63 **Aimoni C**, Bianchini C, Borin M, Ciorba A, Fellin R, Martini A, Scanelli G, Volpato S. Diabetes, cardiovascular risk factors and idiopathic sudden sensorineural hearing loss: a case-control study. *Audiol Neurootol* 2010; **15**: 111-115 [PMID: 19657186 DOI: 10.1159/000231636]
64 **Gäckler A**, Eickelmann AK, Brors D, Dazert S, Epplen JT, Kunstmann E. Positive family history of idiopathic sudden sensorineural hearing loss. *Eur Arch Otorhinolaryngol* 2010; **267**: 1843-1848 [PMID: 20593290 DOI: 10.1007/s00405-010-1310-3]
65 **Lin HC**, Chao PZ, Lee HC. Sudden sensorineural hearing loss increases the risk of stroke: a 5-year follow-up study. *Stroke* 2008; **39**: 2744-2748 [PMID: 18583554 DOI: 10.1161/STROKEAHA.108.519090]
66 **Nishio N**, Teranishi M, Uchida Y, Sugiura S, Ando F, Shimokata H, Sone M, Otake H, Kato K, Yoshida T, Tagaya M, Hibi T, Nakashima T. Polymorphisms in genes encoding aquaporins 4 and 5 and estrogen receptor α in patients with Ménière's disease and sudden sensorineural hearing loss. *Life Sci* 2013; **92**: 541-546 [PMID: 23352976 DOI: 10.1016/j.lfs.2013.01.019]
67 **Haubner F**, Rohrmeier C, Koch C, Vielsmeier V, Strutz J, Kleinjung T. Occurence of a round window membrane rupture in patients with sudden sensorineural hearing loss. *BMC Ear Nose Throat Disord* 2012; **12**: 14 [PMID: 23194317 DOI: 10.1186/1472-6815-12-14]
68 **Chen X**, Zhang XD, Gu X, Fang ZM, Zhang R. Endolymphatic space imaging in idiopathic sudden sensorineural hearing loss with vertigo. *Laryngoscope* 2012; **122**: 2265-2268 [PMID: 22996668 DOI: 10.1002/lary.23452]
69 **Park JJ**, Luedeke I, Luecke K, Emmerling O, Westhofen M. Eustachian tube function in patients with inner ear disorders. *Eur Arch Otorhinolaryngol* 2013; **270**: 1615-1621 [PMID: 22941437 DOI: 10.1007/s00405-012-2143-z]
70 **Punj J**, Pandey R, Darlong V. Sensorineural hearing loss after general anaesthesia: 52 cases reported until now! *Anaesthesia* 2009; **64**: 226 [PMID: 19143715 DOI: 10.1111/j.1365-2044.2008.05846.x]
71 **Lin HC**, Lee HC, Chao PZ, Wu CS. The effects of weather on the incidence of sudden sensorineural hearing loss: a 5-year population-based study. *Audiol Neurootol* 2006; **11**: 165-171 [PMID: 16462137 DOI: 10.1159/000091268]
72 **Amor-Dorado JC**, Paco L, Martin J, Lopez-Nevot MA, Gonzalez-Gay MA. Human leukocyte antigen-DQB1 and -DRB1 associations in patients with idiopathic sudden sensorineural hearing loss from a defined population of Northwest Spain. *Acta Otolaryngol* 2005; **125**: 1277-1282 [PMID: 16303674 DOI: 10.1080/00016480510012228]
73 **Danielides V**, Nousia CS, Bartzokas A, Lolis CJ, Kateri M, Skevas A. Weather conditions and sudden sensorineural hearing loss. *BMC Ear Nose Throat Disord* 2002; **2**: 2 [PMID: 12123526]
74 **Finger RP**, Gostian AO. Idiopathic sudden hearing loss: contradictory clinical evidence, placebo effects and high spontaneous recovery rate--where do we stand in assessing treatment outcomes? *Acta Otolaryngol* 2006; **126**: 1124-1127 [PMID: 17043035 DOI: 10.1080/00016480600702084]
75 **Nosrati-Zarenoe R**, Arlinger S, Hultcrantz E. Idiopathic sudden sensorineural hearing loss: results drawn from the Swedish national database. *Acta Otolaryngol* 2007; **127**: 1168-1175 [PMID: 17851927 DOI: 10.1080/00016480701242477]
76 **Adams JC**. Clinical implications of inflammatory cytokines in the cochlea: a technical note. *Otol Neurotol* 2002; **23**: 316-322 [PMID: 11981388]
77 **Mattson MP**, Culmsee C, Yu Z, Camandola S. Roles of nuclear factor kappaB in neuronal survival and plasticity. *J Neurochem* 2000; **74**: 443-456 [PMID: 10646495]
78 **Selye H**, Fortier C. Adaptive reactions to stress. *Res Publ Assoc Res Nerv Ment Dis* 1949; **29**: 3-18 [PMID: 14854281]
79 **Selye H**, McKeown T. Studies on the physiology of the maternal placenta in the rat. *Proc Roy Soc Lond* 1935; **119**: 1-35
80 **Selye H**, Bajusz E. Sensitization by potassium deficiency for the production of myocardial necrosis by stress. *Am J Pathol* 1959; **35**: 525-535 [PMID: 13649885]
81 **Grippo AJ**, Johnson AK. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. *Stress* 2009; **12**: 1-21 [PMID: 19116888 DOI: 10.1080/10253890802046281]
82 **Hall JM**, Cruser D, Podawiltz A, Mummert DI, Jones H, Mummert ME. Psychological Stress and the Cutaneous Immune Response: Roles of the HPA Axis and the Sympathetic Nervous System in Atopic Dermatitis and Psoriasis. *Dermatol Res Pract* 2012; **2012**: 403908 [PMID: 22969795 DOI: 10.1155/2012/403908]
83 **Gold PW**, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Mol Psychiatry* 2002; **7**: 254-275 [PMID: 11920153 DOI: 10.1038/sj.mp.4001032]
84 **Cohen S**, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, Turner RB. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proc Natl Acad Sci USA* 2012; **109**: 5995-5999 [PMID: 22474371 DOI: 10.1073/pnas.1118355109]
85 **Khan KM**, Drescher MJ, Hatfield JS, Ramakrishnan NA, Drescher DG. Immunohistochemical localization of adrenergic receptors in the rat organ of corti and spiral ganglion. *J Neurosci Res* 2007; **85**: 3000-3012 [PMID: 17671986 DOI: 10.1002/jnr.21404]
86 **Khan KM**, Sarfaraz N, Siddiqui S, Malik ZA, Salim Z. Expression of G protein alpha subunits in the lateral wall of the rat cochlea. *J Anat* 2003; **202**: 293-301 [PMID: 12713269]
87 **Gruber DD**, Dang H, Shimozono M, Scofield MA, Wangemann P. Alpha1A-adrenergic receptors mediate vasoconstriction of the isolated spiral modiolar artery in vitro. *Hear Res* 1998; **119**: 113-124 [PMID: 9641324]
88 **Ross MD**. Glycogen accumulation in Reissner's membrane following chemical sympathectomy with 6-hydroxydopamine. *Acta Otolaryngol* 1978; **86**: 314-330 [PMID: 213930]
89 **Wangemann P**, Liu J, Shimozono M, Schimanski S, Scofield MA. K+ secretion in strial marginal cells is stimulated via beta 1-adrenergic receptors but not via beta 2-adrenergic or vasopressin receptors. *J Membr Biol* 2000; **175**: 191-202 [PMID: 10833529]
90 **Fauser C**, Schimanski S, Wangemann P. Localization of beta1-adrenergic receptors in the cochlea and the vestibular labyrinth. *J Membr Biol* 2004; **201**: 25-32 [PMID: 15635809]
91 **Mori N**, Uozumi N. Evidence that beta 2-receptors mediate action of catecholamines on endolymphatic sac DC potential. *Am J Physiol* 1991; **260**: R911-R915 [PMID: 1852128]
92 **Schimanski S**, Scofield MA, Wangemann P. Functional beta2-adrenergic receptors are present in nonstrial tissues of the lateral wall in the gerbil cochlea. *Audiol Neurootol* 2001; **6**: 124-131 [PMID: 11474138]
93 **Khan KM**, Drescher MJ, Hatfield JS, Khan AM, Drescher DG. Muscarinic receptor subtypes are differentially distributed in the rat cochlea. *Neuroscience* 2002; **111**: 291-302 [PMID: 11983315]
94 **Kanzaki J**, Masuda M. Correlation between stress and acute sensorineural hearing loss: stress and sudden deafness (in Japanese). *Audiology Japan* 2013; **56**: 137-152
95 **Rosas-Ballina M**, Olofsson PS, Ochani M, Valdés-Ferrer SI, Levine YA, Reardon C, Tusche MW, Pavlov VA, Andersson U, Chavan S, Mak TW, Tracey KJ. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. *Science* 2011; **334**: 98-101 [PMID: 21921156 DOI: 10.1126/science.1209985]
96 **Dimitrijevic M**, Stanojevic S, Kustrimovic N, Leposavic G. End-point effector stress mediators in neuroimmune interactions: their role in immune system homeostasis and autoim-

mune pathology. *Immunol Res* 2012; **52**: 64-80 [PMID: 22396175 DOI: 10.1007/s12026-012-8275-9]
97 **Dragoş D**, Tănăsescu MD. The effect of stress on the defense systems. *J Med Life* 2010; **3**: 10-18 [PMID: 20302192]
98 **Shi FD**, Ljunggren HG, Sarvetnick N. Innate immunity and autoimmunity: from self-protection to self-destruction. *Trends Immunol* 2001; **22**: 97-101 [PMID: 11286711]
99 **Costantini C**, Micheletti A, Calzetti F, Perbellini O, Pizzolo G, Cassatella MA. Neutrophil activation and survival are modulated by interaction with NK cells. *Int Immunol* 2010; **22**: 827-838 [PMID: 20739460 DOI: 10.1093/intimm/dxq434]
100 **King PT**, Ngui J, Farmer MW, Hutchinson P, Holmes PW, Holdsworth SR. Cytotoxic T lymphocyte and natural killer cell responses to non-typeable Haemophilus influenzae. *Clin Exp Immunol* 2008; **152**: 542-551 [PMID: 18462210 DOI: 10.1111/j.1365-2249.2008.03667.x]
101 **Shi FD**, Zhou Q. Natural killer cells as indispensable players and therapeutic targets in autoimmunity. *Autoimmunity* 2011; **44**: 3-10 [PMID: 20701455 DOI: 10.3109/08916931003782122]
102 **Cohen F**, Kemeny ME, Zegans LS, Johnson P, Kearney KA, Stites DP. Immune function declines with unemployment and recovers after stressor termination. *Psychosom Med* 2007; **69**: 225-234 [PMID: 17401058 DOI: 10.1097/PSY.0b013e31803139a6]
103 **Borella P**, Bargellini A, Rovesti S, Pinelli M, Vivoli R, Solfrini V, Vivoli G. Emotional stability, anxiety, and natural killer activity under examination stress. *Psychoneuroendocrinology* 1999; **24**: 613-627 [PMID: 10399771]
104 **Fletcher MA**, Zeng XR, Maher K, Levis S, Hurwitz B, Antoni M, Broderick G, Klimas NG. Biomarkers in chronic fatigue syndrome: evaluation of natural killer cell function and dipeptidyl peptidase IV/CD26. *PLoS One* 2010; **5**: e10817 [PMID: 20520837 DOI: 10.1371/journal.pone.0010817]
105 **Fondell E**, Axelsson J, Franck K, Ploner A, Lekander M, Bälter K, Gaines H. Short natural sleep is associated with higher T cell and lower NK cell activities. *Brain Behav Immun* 2011; **25**: 1367-1375 [PMID: 21496482 DOI: 10.1016/j.bbi.2011.04.004]
106 **Bellingrath S**, Rohleder N, Kudielka BM. Healthy working school teachers with high effort-reward-imbalance and overcommitment show increased pro-inflammatory immune activity and a dampened innate immune defence. *Brain Behav Immun* 2010; **24**: 1332-1339 [PMID: 20599495 DOI: 10.1016/j.bbi.2010.06.011]
107 **Rohleder N**, Aringer M, Boentert M. Role of interleukin-6 in stress, sleep, and fatigue. *Ann N Y Acad Sci* 2012; **1261**: 88-96 [PMID: 22823398 DOI: 10.1111/j.1749-6632.2012.06634.x]
108 **Goshen I**, Yirmiya R. Interleukin-1 (IL-1): a central regulator of stress responses. *Front Neuroendocrinol* 2009; **30**: 30-45 [PMID: 19017533 DOI: 10.1016/j.yfrne.2008.10.001]
109 **Elenkov IJ**, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve--an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev* 2000; **52**: 595-638 [PMID: 11121511]
110 **Gadek-Michalska A**, Spyrka J, Bugajski J. Psychosocial stress affects the involvement of prostaglandins and nitric oxide in the lipopolysaccharide-induced hypothalamic-pituitary-adrenal response. *J Physiol Pharmacol* 2005; **56**: 287-298 [PMID: 15985709]
111 **Dinarello CA**, Simon A, van der Meer JW. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nat Rev Drug Discov* 2012; **11**: 633-652 [PMID: 22850787 DOI: 10.1038/nrd3800]
112 **Bellingrath S**, Rohleder N, Kudielka BM. Effort-reward-imbalance in healthy teachers is associated with higher LPS-stimulated production and lower glucocorticoid sensitivity of interleukin-6 in vitro. *Biol Psychol* 2013; **92**: 403-409 [PMID: 23246534 DOI: 10.1016/j.biopsycho.2012.12.003]
113 **Scheller J**, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochim Biophys Acta* 2011; **1813**: 878-888 [PMID: 21296109 DOI: 10.1016/j.bbamcr.2011.01.034]
114 **Bierhaus A**, Wolf J, Andrassy M, Rohleder N, Humpert PM, Petrov D, Ferstl R, von Eynatten M, Wendt T, Rudofsky G, Joswig M, Morcos M, Schwaninger M, McEwen B, Kirschbaum C, Nawroth PP. A mechanism converting psychosocial stress into mononuclear cell activation. *Proc Natl Acad Sci USA* 2003; **100**: 1920-1925 [PMID: 12578963 DOI: 10.1073/pnas.0438019100]
115 **Pace TW**, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, Heim CM. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am J Psychiatry* 2006; **163**: 1630-1633 [PMID: 16946190 DOI: 10.1176/appi.ajp.163.9.1630]
116 **Richlin VA**, Arevalo JM, Zack JA, Cole SW. Stress-induced enhancement of NF-kappaB DNA-binding in the peripheral blood leukocyte pool: effects of lymphocyte redistribution. *Brain Behav Immun* 2004; **18**: 231-237 [PMID: 15050650 DOI: 10.1016/j.bbi.2003.08.001]
117 **Iliopoulos D**, Jaeger SA, Hirsch HA, Bulyk ML, Struhl K. STAT3 activation of miR-21 and miR-181b-1 via PTEN and CYLD are part of the epigenetic switch linking inflammation to cancer. *Mol Cell* 2010; **39**: 493-506 [PMID: 20797623 DOI: 10.1016/j.molcel.2010.07.023]
118 **Jeong HJ**, Hong SH, Park RK, Shin T, An NH, Kim HM. Hypoxia-induced IL-6 production is associated with activation of MAP kinase, HIF-1, and NF-kappaB on HEI-OC1 cells. *Hear Res* 2005; **207**: 59-67 [PMID: 15913932 DOI: 10.1016/j.heares.2005.04.003]
119 **Rief W**, Mills PJ, Ancoli-Israel S, Ziegler MG, Pung MA, Dimsdale JE. Overnight changes of immune parameters and catecholamines are associated with mood and stress. *Psychosom Med* 2010; **72**: 755-762 [PMID: 20841563 DOI: 10.1097/PSY.0b013e3181f367e2]
120 **Chennaoui M**, Sauvet F, Drogou C, Van Beers P, Langrume C, Guillard M, Gourby B, Bourrilhon C, Florence G, Gomez-Merino D. Effect of one night of sleep loss on changes in tumor necrosis factor alpha (TNF-α) levels in healthy men. *Cytokine* 2011; **56**: 318-324 [PMID: 21737301 DOI: 10.1016/j.cyto.2011.06.002]
121 **von Känel R**, Bellingrath S, Kudielka BM. Association between burnout and circulating levels of pro- and anti-inflammatory cytokines in schoolteachers. *J Psychosom Res* 2008; **65**: 51-59 [PMID: 18582612 DOI: 10.1016/j.jpsychores.2008.02.007]
122 **Lalive PH**, Burkhard PR, Chofflon M. TNF-alpha and psychologically stressful events in healthy subjects: potential relevance for multiple sclerosis relapse. *Behav Neurosci* 2002; **116**: 1093-1097 [PMID: 12492308]
123 **Weber C**, Arck P, Mazurek B, Klapp BF. Impact of a relaxation training on psychometric and immunologic parameters in tinnitus sufferers. *J Psychosom Res* 2002; **52**: 29-33 [PMID: 11801262]
124 **Mommersteeg PM**, Pelle AJ, Ramakers C, Szabó BM, Denollet J, Kupper N. Type D personality and course of health status over 18 months in outpatients with heart failure: multiple mediating inflammatory biomarkers. *Brain Behav Immun* 2012; **26**: 301-310 [PMID: 21983280 DOI: 10.1016/j.bbi.2011.09.010]
125 **Heinrich UR**, Helling K. Nitric oxide--a versatile key player in cochlear function and hearing disorders. *Nitric Oxide* 2012; **27**: 106-116 [PMID: 22659013 DOI: 10.1016/j.niox.2012.05.005]
126 **Kerr PM**, Tam R, Narang D, Potts K, McMillan D, McMillan K, Plane F. Endothelial calcium-activated potassium channels as therapeutic targets to enhance availability of nitric oxide. *Can J Physiol Pharmacol* 2012; **90**: 739-752 [PMID: 22626011 DOI: 10.1139/y2012-075]
127 **Keynes RG**, Garthwaite J. Nitric oxide and its role in ischaemic brain injury. *Curr Mol Med* 2004; **4**: 179-191 [PMID: 15032712]
128 **Zhao HB**, Kikuchi T, Ngezahayo A, White TW. Gap junctions and cochlear homeostasis. *J Membr Biol* 2006; **209**: 177-186 [PMID: 16773501 DOI: 10.1007/s00232-005-0832-x]
129 **Kikuchi T**, Kimura RS, Paul DL, Adams JC. Gap junctions in

the rat cochlea: immunohistochemical and ultrastructural analysis. *Anat Embryol* (Berl) 1995; **191**: 101-118 [PMID: 7726389]
130 **Spicer SS**, Schulte BA. Differentiation of inner ear fibrocytes according to their ion transport related activity. *Hear Res* 1991; **56**: 53-64 [PMID: 1663106]
131 **Hirose K**, Liberman MC. Lateral wall histopathology and endocochlear potential in the noise-damaged mouse cochlea. *J Assoc Res Otolaryngol* 2003; **4**: 339-352 [PMID: 14690052 DOI: 10.1007/s10162-002-3036-4]
132 **Kelly JJ**, Forge A, Jagger DJ. Development of gap junctional intercellular communication within the lateral wall of the rat cochlea. *Neuroscience* 2011; **180**: 360-369 [PMID: 21320575 DOI: 10.1016/j.neuroscience.2011.02.011]
133 **Suzuki T**, Matsunami T, Hisa Y, Takata K, Takamatsu T, Oyamada M. Roles of gap junctions in glucose transport from glucose transporter 1-positive to -negative cells in the lateral wall of the rat cochlea. *Histochem Cell Biol* 2009; **131**: 89-102 [PMID: 18787834 DOI: 10.1007/s00418-008-0502-z]
134 **Kelly JJ**, Forge A, Jagger DJ. Contractility in type III cochlear fibrocytes is dependent on non-muscle myosin II and intercellular gap junctional coupling. *J Assoc Res Otolaryngol* 2012; **13**: 473-484 [PMID: 22476723 DOI: 10.1007/s10162-012-0322-7]
135 **Hibino H**, Nin F, Tsuzuki C, Kurachi Y. How is the highly positive endocochlear potential formed? The specific architecture of the stria vascularis and the roles of the ion-transport apparatus. *Pflugers Arch* 2010; **459**: 521-533 [PMID: 20012478 DOI: 10.1007/s00424-009-0754-z]
136 **Hequembourg S**, Liberman MC. Spiral ligament pathology: a major aspect of age-related cochlear degeneration in C57BL/6 mice. *J Assoc Res Otolaryngol* 2001; **2**: 118-129 [PMID: 11550522]
137 **Hoya N**, Okamoto Y, Kamiya K, Fujii M, Matsunaga T. A novel animal model of acute cochlear mitochondrial dysfunction. *Neuroreport* 2004; **15**: 1597-1600 [PMID: 15232290]
138 **Mizutari K**, Matsunaga T, Kamiya K, Fujinami Y, Fujii M, Ogawa K. Caspase inhibitor facilitates recovery of hearing by protecting the cochlear lateral wall from acute cochlear mitochondrial dysfunction. *J Neurosci Res* 2008; **86**: 215-222 [PMID: 17722114 DOI: 10.1002/jnr.21470]
139 **Okamoto Y**, Hoya N, Kamiya K, Fujii M, Ogawa K, Matsunaga T. Permanent threshold shift caused by acute cochlear mitochondrial dysfunction is primarily mediated by degeneration of the lateral wall of the cochlea. *Audiol Neurootol* 2005; **10**: 220-233 [PMID: 15809501 DOI: 10.1159/000084843]
140 **Wang Y**, Hirose K, Liberman MC. Dynamics of noise-induced cellular injury and repair in the mouse cochlea. *J Assoc Res Otolaryngol* 2002; **3**: 248-268 [PMID: 12382101 DOI: 10.1007/s101620020028]
141 **Adams JC**, Seed B, Lu N, Landry A, Xavier RJ. Selective activation of nuclear factor kappa B in the cochlea by sensory and inflammatory stress. *Neuroscience* 2009; **160**: 530-539 [PMID: 19285117]
142 **Yamamoto H**, Omelchenko I, Shi X, Nuttall AL. The influence of NF-kappaB signal-transduction pathways on the murine inner ear by acoustic overstimulation. *J Neurosci Res* 2009; **87**: 1832-1840 [PMID: 19185019 DOI: 10.1002/jnr.22018]
143 **Miyao M**, Firestein GS, Keithley EM. Acoustic trauma augments the cochlear immune response to antigen. *Laryngoscope* 2008; **118**: 1801-1808 [PMID: 18806477 DOI: 10.1097/MLG.0b013e31817e2c27]
144 **Masuda M**, Nagashima R, Kanzaki S, Fujioka M, Ogita K, Ogawa K. Nuclear factor-kappa B nuclear translocation in the cochlea of mice following acoustic overstimulation. *Brain Res* 2006; **1068**: 237-247 [PMID: 16376312]
145 **So H**, Kim H, Lee JH, Park C, Kim Y, Kim E, Kim JK, Yun KJ, Lee KM, Lee HY, Moon SK, Lim DJ, Park R. Cisplatin cytotoxicity of auditory cells requires secretions of proinflammatory cytokines via activation of ERK and NF-kappaB. *J Assoc Res Otolaryngol* 2007; **8**: 338-355 [PMID: 17516123 DOI: 10.1007/s10162-007-0084-9]
146 **Fujioka M**, Kanzaki S, Okano HJ, Masuda M, Ogawa K, Okano H. Proinflammatory cytokines expression in noise-induced damaged cochlea. *J Neurosci Res* 2006; **83**: 575-583 [PMID: 16429448 DOI: 10.1002/jnr.20764]
147 **Rahman A**, Fazal F. Hug tightly and say goodbye: role of endothelial ICAM-1 in leukocyte transmigration. *Antioxid Redox Signal* 2009; **11**: 823-839 [PMID: 18808323 DOI: 10.1089/ARS.2008.2204]
148 **Wagner DD**, Frenette PS. The vessel wall and its interactions. *Blood* 2008; **111**: 5271-5281 [PMID: 18502843 DOI: 10.1182/blood-2008-01-078204]
149 **Sumagin R**, Kuebel JM, Sarelius IH. Leukocyte rolling and adhesion both contribute to regulation of microvascular permeability to albumin via ligation of ICAM-1. *Am J Physiol Cell Physiol* 2011; **301**: C804-C813 [PMID: 21653902 DOI: 10.1152/ajpcell.00135.2011]
150 **Neuser J**, Knoop T. Sudden idiopathic hearing loss: psychopathology and antecedent stressful life-events. *Br J Med Psychol* 1986; **59** (Pt 3): 245-251 [PMID: 3768272]
151 **Nakamura M**, Aoki N, Nakashima T, Hoshino T, Yokoyama T, Morioka S, Kawamura T, Tanaka H, Hashimoto T, Ohno Y, Whitlock G. Smoking, alcohol, sleep and risk of idiopathic sudden deafness: a case-control study using pooled controls. *J Epidemiol* 2001; **11**: 81-86 [PMID: 11388497]
152 **Nakashima T**, Tanabe T, Yanagita N, Wakai K, Ohno Y. Risk factors for sudden deafness: a case-control study. *Auris Nasus Larynx* 1997; **24**: 265-270 [PMID: 9251855]
153 **Merchant SN**, Durand ML, Adams JC. Sudden deafness: is it viral? *ORL J Otorhinolaryngol Relat Spec* 2008; **70**: 52-60; discussion 60-62 [PMID: 18235206 DOI: 10.1159/000111048]
154 **Mazzeo RS**, Donovan D, Fleshner M, Butterfield GE, Zamudio S, Wolfel EE, Moore LG. Interleukin-6 response to exercise and high-altitude exposure: influence of alpha-adrenergic blockade. *J Appl Physiol* 2001; **91**: 2143-2149 [PMID: 11641355]
155 **Mattox DE**, Simmons FB. Natural history of sudden sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 1977; **86**: 463-480 [PMID: 889223]
156 **Eisenberger NI**, Inagaki TK, Mashal NM, Irwin MR. Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood. *Brain Behav Immun* 2010; **24**: 558-563 [PMID: 20043983 DOI: 10.1016/j.bbi.2009.12.009]
157 **Kimbrell MR**, Warshakoon H, Cromer JR, Malladi S, Hood JD, Balakrishna R, Scholdberg TA, David SA. Comparison of the immunostimulatory and proinflammatory activities of candidate Gram-positive endotoxins, lipoteichoic acid, peptidoglycan, and lipopeptides, in murine and human cells. *Immunol Lett* 2008; **118**: 132-141 [PMID: 18468694 DOI: 10.1016/j.imlet.2008.03.009]
158 **Suwa T**, Hogg JC, English D, Van Eeden SF. Interleukin-6 induces demargination of intravascular neutrophils and shortens their transit in marrow. *Am J Physiol Heart Circ Physiol* 2000; **279**: H2954-H2960 [PMID: 11087252]
159 **Wolters PJ**, Wray C, Sutherland RE, Kim SS, Koff J, Mao Y, Frank JA. Neutrophil-derived IL-6 limits alveolar barrier disruption in experimental ventilator-induced lung injury. *J Immunol* 2009; **182**: 8056-8062 [PMID: 19494331 DOI: 10.4049/jimmunol.0801323]
160 **Nijm J**, Wikby A, Tompa A, Olsson AG, Jonasson L. Circulating levels of proinflammatory cytokines and neutrophil-platelet aggregates in patients with coronary artery disease. *Am J Cardiol* 2005; **95**: 452-456 [PMID: 15695127 DOI: 10.1016/j.amjcard.2004.10.009]
161 **Khuseyinova N**, Koenig W. Biomarkers of outcome from cardiovascular disease. *Curr Opin Crit Care* 2006; **12**: 412-419 [PMID: 16943718 DOI: 10.1097/01.ccx.0000244119.16377.75]
162 **Maugeri N**, Manfredi AA, Maseri A. Clinical and experimental evidences on the prothrombotic properties of neutrophils. *Srp Arh Celok Lek* 2010; **138** Suppl 1: 50-52 [PMID: 20229683]
163 **Wakabayashi K**, Fujioka M, Kanzaki S, Okano HJ, Shibata S, Yamashita D, Masuda M, Mihara M, Ohsugi Y, Ogawa K,

Okano H. Blockade of interleukin-6 signaling suppressed cochlear inflammatory response and improved hearing impairment in noise-damaged mice cochlea. *Neurosci Res* 2010; **66**: 345-352 [PMID: 20026135 DOI: 10.1016/j.neures.2009.12.008]

164 **Scherer EQ**, Yang J, Canis M, Reimann K, Ivanov K, Diehl CD, Backx PH, Wier WG, Strieth S, Wangemann P, Voigtlaender-Bolz J, Lidington D, Bolz SS. Tumor necrosis factor-α enhances microvascular tone and reduces blood flow in the cochlea via enhanced sphingosine-1-phosphate signaling. *Stroke* 2010; **41**: 2618-2624 [PMID: 20930159 DOI: 10.1161/STROKEAHA.110.593327]

165 **Wang Y**, Yu C, Pan Y, Li J, Zhang Y, Ye F, Yang S, Zhang H, Li X, Liang G. A novel compound C12 inhibits inflammatory cytokine production and protects from inflammatory injury in vivo. *PLoS One* 2011; **6**: e24377 [PMID: 21931698 DOI: 10.1371/journal.pone.0024377]

166 **Maruo N**, Morita I, Shirao M, Murota S. IL-6 increases endothelial permeability in vitro. *Endocrinology* 1992; **131**: 710-714 [PMID: 1639018]

167 **Gyo K**. Experimental study of transient cochlear ischemia as a cause of sudden deafness. *World J Otorhinolaryngol* 2013; **3**: 1-15 [DOI: 10.5319/wjo.v3.i1.1]

168 **Sugiura M**, Naganawa S, Teranishi M, Nakashima T. Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging findings in patients with sudden sensorineural hearing loss. *Laryngoscope* 2006; **116**: 1451-1454 [PMID: 16885752 DOI: 10.1097/01.mlg.0000228005.78187.23]

169 **Yoshida T**, Sugiura M, Naganawa S, Teranishi M, Nakata S, Nakashima T. Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging findings and prognosis in sudden sensorineural hearing loss. *Laryngoscope* 2008; **118**: 1433-1437 [PMID: 18475208 DOI: 10.1097/MLG.0b013e318172ef85]

170 **Ryu IS**, Yoon TH, Ahn JH, Kang WS, Choi BS, Lee JH, Shim MJ. Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging in sudden sensorineural hearing loss: correlations with audiologic and vestibular testing. *Otol Neurotol* 2011; **32**: 1205-1209 [PMID: 21921851 DOI: 10.1097/MAO.0b013e31822e969f]

171 **Asberg M**, Nygren A, Leopardi R, Rylander G, Peterson U, Wilczek L, Källmén H, Ekstedt M, Akerstedt T, Lekander M, Ekman R. Novel biochemical markers of psychosocial stress in women. *PLoS One* 2009; **4**: e3590 [PMID: 19177163 DOI: 10.1371/journal.pone.0003590]

172 **Jonsdottir IH**, Hägg DA, Glise K, Ekman R. Monocyte chemotactic protein-1 (MCP-1) and growth factors called into question as markers of prolonged psychosocial stress. *PLoS One* 2009; **4**: e7659 [PMID: 19888340 DOI: 10.1371/journal.pone.0007659]

173 **Broderick G**, Fuite J, Kreitz A, Vernon SD, Klimas N, Fletcher MA. A formal analysis of cytokine networks in chronic fatigue syndrome. *Brain Behav Immun* 2010; **24**: 1209-1217 [PMID: 20447453 DOI: 10.1016/j.bbi.2010.04.012]

174 **Kang HS**, Park JJ, Ahn SK, Hur DG, Kim HY. Effect of high dose intravenous vitamin C on idiopathic sudden sensorineural hearing loss: a prospective single-blind randomized controlled trial. *Eur Arch Otorhinolaryngol* 2013; **270**: 2631-2636 [PMID: 23208525 DOI: 10.1007/s00405-012-2294-y]

P- Reviewers Ciuman R, Gross M, Nakashima T
S- Editor Gou SX **L- Editor** A **E- Editor** Zheng XM

百世登
Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com