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

**Masuda M *et al*.** Stress response theory

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**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 kappa-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.

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**Key words:** Cause; Idiopathic sudden sensorineural hearing loss; Lateral wall; Nuclear factor kappa-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.

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**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[1-70]. 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[71]. In fact, Nosrati-Zarenoe *et al*[72] 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 Adams, Merchant and their colleagues[52,73]. They proposed that ISHL might be a result of pathologic activation of nuclear factor kappa-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[74]. 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*[75,76]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*[77] 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)[78-80].

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[81].

***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[78]. 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)[82-91]. 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[92], 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 in section II.

***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[93,94]. Furthermore, there are frequent associations between infectious diseases and autoimmune diseases[95]. The natural killer (NK) cell has critical roles in resistance against both viral and bacterial infections[96,97], and in regulating autoimmunity[98]. However, NK cell activity (NKCA) is reduced by chronic stress like fatigue, stressful life events, inability to cope with stress, and shortness of sleep[99-103]. 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[104-106]. NO is also involved in the HPA axis response[107].

IL-1 is a potent pro-inflammatory cytokine[108], and is produced centrally and periphery following exposure to immunological and psychological stressors[105]. 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[104].

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[104]. 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[109].

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[110].

The underlying mechanism of IL-6 increase under stress is associated with activation of NF-κB[111,112]. Cortisol and catecholamines in the HPA axis and the SNS induce and enhance NF-κB activation under psychosocial stress[111,113]. 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[114,115]. 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[116]. Conversely, IL-6 elevation per se generates fatigue, fever, and sleep-related symptoms such as daytime somnolence[104].

Additionally, TNF-α also increases under chronic psychosocial stress[103,117-120]. There is in fact a personality type associated with high TNF-α, distressed personality[121]. 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[122,123]. It is also involved in the LPS-induced HPA axis response under basal conditions and during its adaptation to chronic social stress circumstances[107]. 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[124].

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[125-128]. They have a critical role in the potassium ion recycling mechanism[129], and could also be implicated in the mechanisms of glucose transport in the cochlea[130]. Type III fibrocytes have even contractility and regulate tension of the basilar membrane, thereby determining auditory sensitivity[131].

In the stria vascularis, there are three types of cells that express multiple ion-transport apparatuses[132]. Therefore, the lateral wall is essential for maintaining cochlear homeostasis, and thus for normal hearing[125,132]. Degeneration of the lateral wall may be implicated in the survival of sensory cells[133].

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

Matsunaga and his colleagues 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)[134-136]. 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 three hours after 3-NP administration[136]. 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[135]. 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*[137] 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)[138-143]. Interestingly, the region where NF-κB is activated changes in the lateral wall depending on the kind of stressor, the degree of the stress intensity, and/or the genetic background of animal.

Adams *et al*[138] demonstrated that NF-κB of type I fibrocytes was mainly activated by an octave-band noise (90-112dB SPL) exposure using CBA/J (Figure 1B). Masuda *et al*[141] 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*[140] 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)[73,138]. Systemic TNF secretion by intraperitoneal anti-CD3 or taxol injection induces the same NF-κB activation as that by LPS[138]. 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[142]. 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 two hours 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)[141]. Using Swiss-Webster mice, the activation was observed four hours after noise exposure but not seven d after[139]. With intraperitoneal LPS, taxol, or anti-CD3 injection, it was observed in the type I fibrocytes of CBA/CaJ mice after 24 h[138].

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 (section I-III). 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[144,145]. They also play an essential role in regulating microvascular permeability[146].

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*[140] 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 four hours after but not seven d after noise-exposure alone. On the other hand, with noise-exposure plus antigen challenge, the activation was observed even seven 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[147-149]. However, this hypothesis has a contradictory survey, as the other hypotheses do (Table 1 and see Merchant *et al*[150]). 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, Adams *et al*[73,138] proposed that the stress response of the lateral wall to systemic stress is the cause of ISHL[52]. They observed the inner ear of a patient who died nine 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[52]. 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[138]. 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*[138] 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 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[138]. 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*[51] 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[111,151], 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[44,47,152].

Infection also enhances immune system dysregulation, cytokine production, and psychological stress[153]. 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[154-156]. 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[157-159]. 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[160]. Circulating TNF-α activates NF-κB of the lateral wall. It also enhances microvascular tone and reduces blood flow in the cochlea[161], 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[162,163], 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[164]. 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[165-167], 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 one or two months in diabetic patients. Monocyte chemotactic protein-1, epidermal growth factor, and vascular endothelial growth factor have been expected to be prolonged psychosocial stress markers[168], but the validity is still controversial[169]. There are controversies about the association of pro-inflammatory cytokines and ISHL as well[30-35,40,51] (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*[170] 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.

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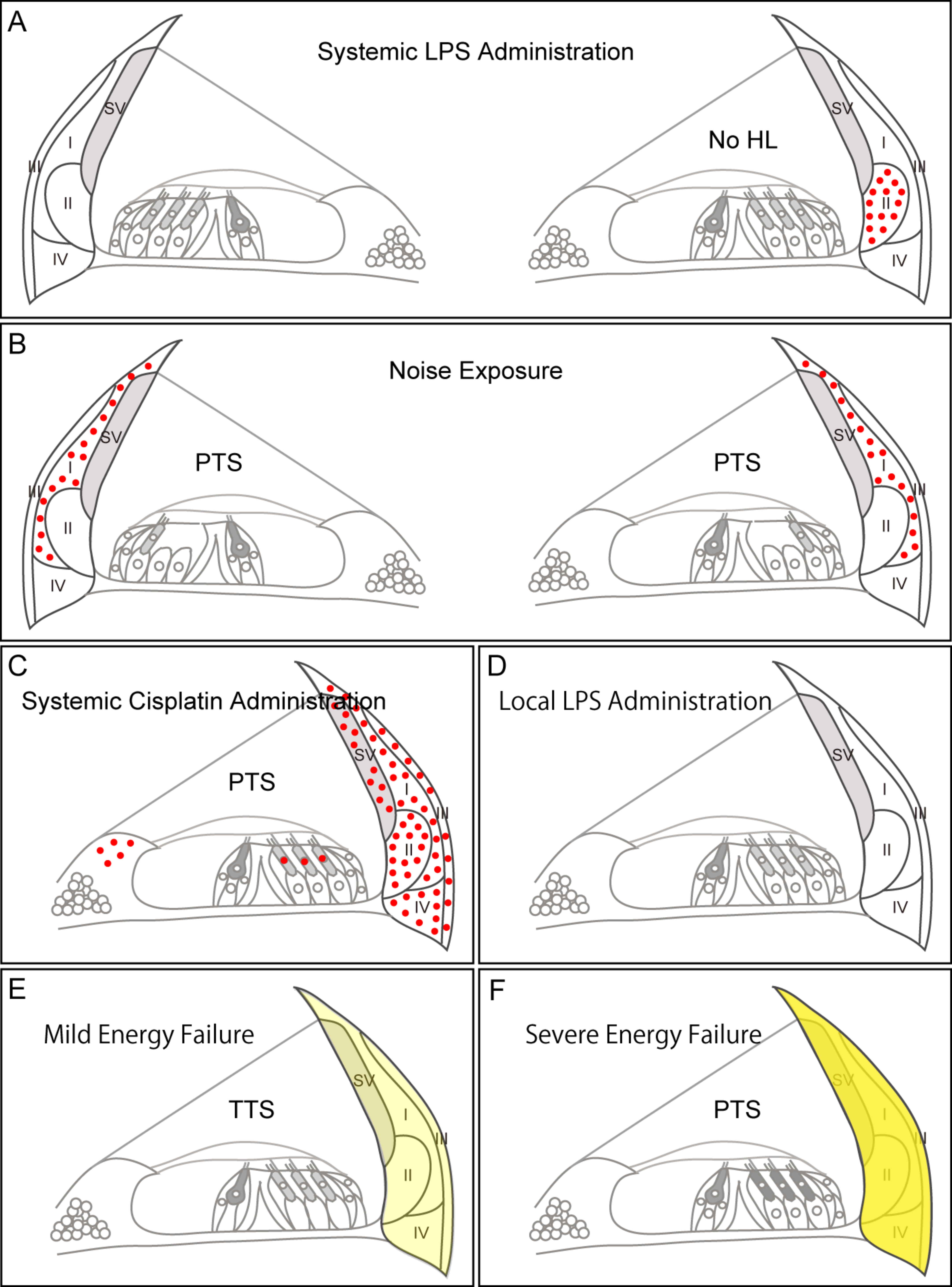
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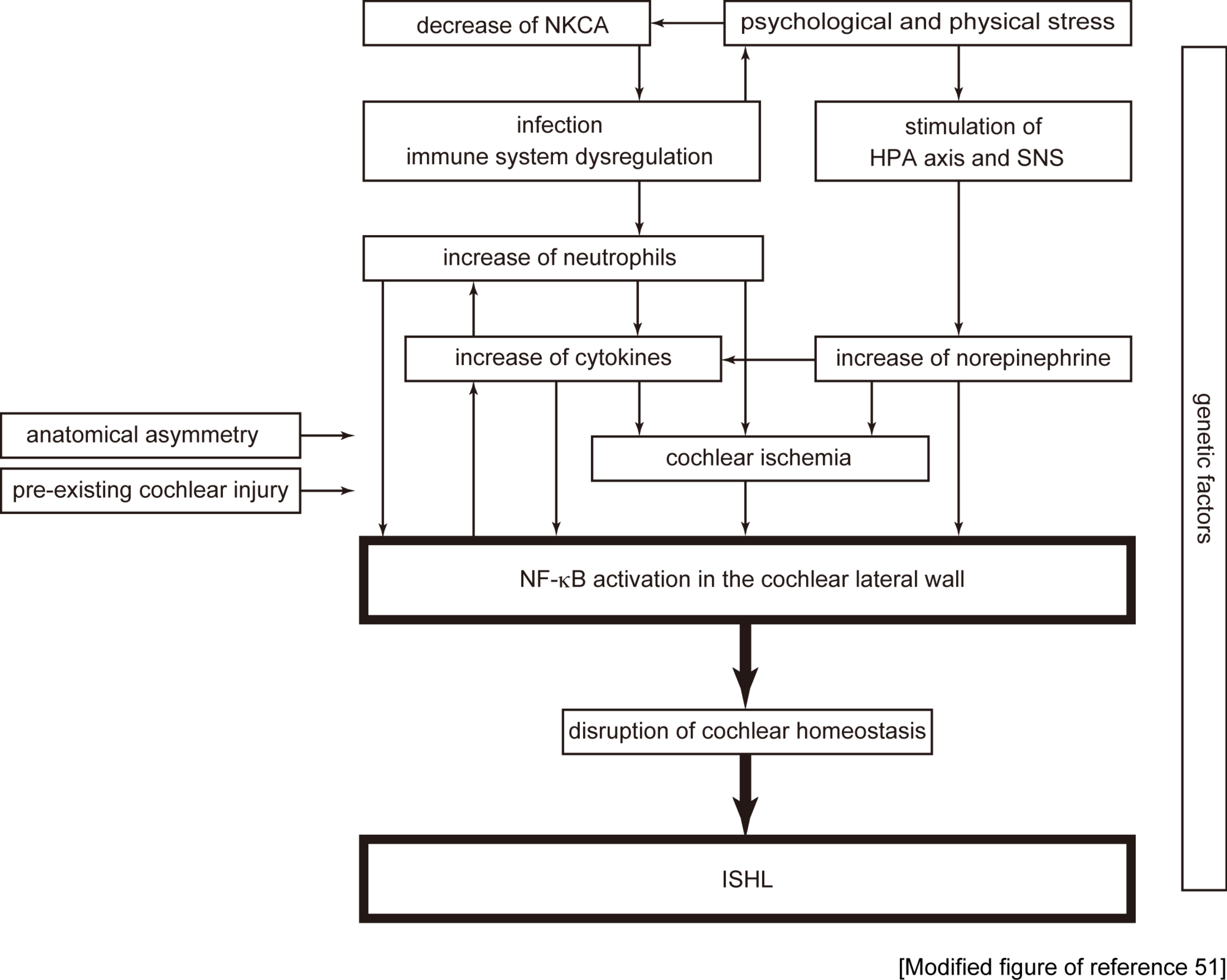
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**Figure 1 Characteristics of the lateral wall stress response.** A-D:The lateral wall is composed of the stria vascularis (SV) and the spiral ligament, in which there are four types of fibrocytes (I-IV). Intraperitoneal lipopolysaccharide (LPS) injection mainly activates nuclear factor kappa-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.



**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.

**Table 1 Potential causes of idiopathic sudden sensorineural hearing loss proposed during this decade**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Main category** | | **Subcategory** | | | **Significantly associated factor** | **NOT significantly associated factor** | **Reference** |
| 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-IMTl, 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 | [41 |
|  | | | FV Leiden poly. | PT poly. | [23] |
| Auto-immunity | | | Cho, homocysteine, PAI-1, anticardiolipin antibodies | FV Leiden poly., FII poly., antithrombin, protein C and S, lupus anticoagulant, lipoprotein(a) | [24] |
| Vascular Impairment　(continued) | |  | eNOS poly. | |  | [25] |
|  | FMD | |  | [26] |
|  | Whole blood viscosity, erythrocyte deformability index, activated clotting time, clot rate, PAI-1 antigen, factor VIII:C | | Plasma viscosity, FG | [27] |
| Auto-immunity | Antiendothelial cell antibody | |  | [28,29] |
| Cytokine | |  | IL-1 B poly., TNF-β poly. | |  | [30,31] |
|  | TNF-α | | IL-10, IL-12 | [32] |
|  | IL-6 poly. | | IL-4R poly., IL-10 poly., TNF-α poly., TNFRSF1B poly., VEGF poly. | [33] |
|  | IL-1A poly. | | IL-1B poly. | [34] |
| Vascular Impairment |  | | IL-6, IL-8, ICAM-1, VCAM-1, E-selectin, MCP-1, lipid, FG, | [35] |
|  | TNF-α, sCD40, sCD40L, T lymphocyte, CD40, cyclooxygenase 2, CD38 positive T or B lymphocyte | | monocyte, macrophage | [36] |
| Cellular Stress | |  | HSP70 poly. | |  | [37] |
|  |  | | GPX1 poli., PON1 poli., PON2 poli., SOD2 poli. | [38] |
|  |  | | GST poly., CYP poly. | [39] |
| Auto-immunity |  | | Anti-HSP 70 antibody, TNF-α, ESR, ANA, antiphospholipid antibody | [40] |
| Auto-immunity | Anti-HSP70antibody, anti-phospholipids antibody | |  | [41] |
|  | HSP70 | |  | [42] |
|  |  | | GST poly. | [43] |
|  | IgA to HSV1 | | IgG and IgM to CMV, VZV, HSV1, and HSV2. IgA to CMV, VZV, and HSV2. |  |
|  |  | | Borrelia | [44] |
|  |  | | Herpes zoster | [45] |
|  | Recent subclinical viral infection (cytomegalovirus, herpes simplex, Epstein-Barr virus), toxoplasmosis infections | |  | [46] |
|  |  | | Enterovirus, cytomegalovirus, Epstein-Barr virus | [47] |
|  |  | | Anti-double stranded DNA, RF, antiphospholipid IgG and M, antinuclear antibody, complements C3 and C4 | [6] |
|  | T cell responding to cochlin | |  | [48] |
|  | Neutrophil, NKCA, IL-6 | | TNF, hCRP | [49] |
|  | Histological evidence of severe osmotic stress of the organ of Corti | |  | [50] |
| Vascular Impairment | AMI | |  | [53] |
|  | Migraine with HT | |  | [54] |
| Vascular Impairment | ED | |  | [55] |
| Vascular Impairment | DM | |  | [51] |
|  | Chronic kidney disease with and without DM | |  | [52] |
|  | Allergy | |  | [56] |
|  | Male with OSA | | Female with OSA | [57] |
| Vascular Impairment | CardioV risk factors, DM, Cho | |  | [58] |
|  | Family history of ISHL | |  | [59] |
| Vascular Impairment | CerebroV stroke | |  | [60] |
|  |  | | Aquaporin 4 and 5 poly., estrogen receptor α poly. | [7] |
|  | Round window membrane rupture | |  | [61] |
|  | Endolymphatic hydrops | |  | [62] |
|  |  | | Eustachian tube dysfunction | [63] |
|  | General anesthesia | |  | [64] |
|  |  | | Month, weather | [65] |
|  | HLA-DQB1 and -DRB1 | |  | [66] |
|  |  | | Season, weather | [67] |

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*[171] 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** | **1β** | **M1** | **M2** | **M3** | **M5** |
| IHC | ○ |  | ○ |  |  | ○ |  | ○ | ○ |
| OHC | ○ |  | ○ |  |  | ○ |  | ○ |  |
| Deiters' cells |  |  | ○ | ○ |  | ○ | ○ | ○ | ○ |
| Hensen's cells |  |  | ○ | ○ |  |  |  |  |  |
| Outer sulcus |  |  | ○ |  |  |  |  |  |  |
| Stria vascularis2 |  |  |  | ○ |  |  |  |  |  |
| Strial marginal cell |  |  | ○ |  |  |  |  |  | ○ |
| capillaries in the stria vascularis |  |  |  |  |  |  |  | ○ |  |
| Spiral ligament2 |  |  | ○ | ○ |  | ○ | ○ | ○ | ○ |
| Rissener's membrane |  |  |  |  | ○ |  |  |  |  |
| Spiral ganglion | ○ |  | ○ | ○ |  | ○ |  | ○ | ○ |
| Nerve fibers approaching HCs | ○ |  | ○ | ○ |  |  |  |  |  |
| Efferent fibers of the intraganglionic spiral bundle |  |  |  |  |  |  | ○ |  | ○ |
| Spiral modiolar artery | ○ | ○ |  |  |  |  |  |  |  |
| Endolymphatic sac |  |  |  | ○ |  |  |  |  |  |

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

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

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **NF-κB** | | **Other factors** | | |  |
| **Animal** | **Stressor** | **Time point** | **Response** | **Location** | **Factor** | **Response** | **Location** | **Reference** |
| CBA/CaJ mice | LPS, *ip* | 24 h | Activation | Unilateral, II >> I, Lim |  |  |  | [135] |
| 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 |  |  |  | [136] |
| 2-12 h1(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 | 2Expression | 3SL | [137] |
| 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 | 2Expression | LW |
| ICAM-1 | Expression | II |
| 118 dB SPL + Ag | 4 h | Activation | I, II, IV, HC, SC |  |  |  |
| 7d | Activation | HC, SC | leukocytes | Expression | 4LW |
| Activation | ICAM-1 | Expression | 4II, III >> I |
| C57/Bl6J mice | 124 dB SPL | 2 h | Activation | I, II, III, IV, SV | iNOS | Most of NF-κB activated cells |  | [138] |
| 72 h | Activation | 5I, II, III, IV, SV | iNOS | 5Most of NF-κB activated cells |  |
| Sprague-Dawley rats | Cisplatin, *ip* | 24 h | Activation | I, II, III, IV, SV, OHC, Lim. | IL-1β | Expression | II, IV >> I, III, SMV | [139] |
| 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 | whole cochlea |
| IL-6 | No expression, no transcription | whole cochlea |
| TNF-α | No expression, no transcription | whole cochlea |
| Sprague-Dawley rats | 124 dB SPL | 3 h |  |  | IL-6 | Expression | III, IV | [140] |
| 6 h |  |  | Expression | I, II, III, IV |
| 12 h |  |  | Expression | I, II, III, IV, SV, SG |
| 24 h |  |  | Expression | 6I, II, III, IV, SG |

1The time in the　parentheses is the time of the maximum up-regulation of a factor; 2The 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; 3There were a small number of leukocytes in the spiral ligament. 4The 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; 5The intensity at 72 h was weaker than at 2 h; 6The intensity at 24 h was much weaker than at 12 h in the lateral wall. Some papers demonstrated nuclear factor kappa-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.