Neurobiology of Stress-Induced Tinnitus

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Contents

Abstract Emotional stress has accompanied humans since the dawn of time and has played an essential role not only in positive selection and adaptation to an ever-changing environment, but also in the acceleration or even initiation of many illnesses. The three main somatic mechanisms induced by stress are the hypothalamus-pituitary-adrenal axis (HPA axis), the sympathetic-adreno-medullar (SAM) axis, and the immune axis. In this chapter, the stress-induced mechanisms that can affect cochlear physiology are presented and discussed in the context of tinnitus generation and auditory neurobiology. It is concluded that all of the presented mechanisms need to be further investigated. It is advised that clinical

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practitioners ask patients about stressful events or chronic stress preceding the tinnitus onset and measure the vital signs. Finally, taking into account that tinnitus itself acts as a stressor, the implementation of anti-stress therapies for tinnitus treatment is recommended.

Keywords Catecholamines · Cytokines · Glucocorticoids · Glutamate excitotoxicity · HPA axis · Immune axis · SAM axis · The cochlea

1 Introduction

The association between emotional stress and tinnitus has long been known, appearing in medical journals for at least 200 years ago (Curtis 1841). The crosstalk between tinnitus and stress is still a subject of intense research (Szczepek and Mazurek 2017; Aydin and Searchfield 2019; Biehl et al. 2019; Brueggemann et al. 2019; Moossavi et al. 2019). An epidemiological study with 12,166 subjects demonstrated that the correlation between tinnitus incidence and stress is as strong as between tinnitus and noise exposure (Baigi et al. 2011). The authors of another study that involved 658 tinnitus patients demonstrated a direct effect of stress level on tinnitus loudness and tinnitus distress (Probst et al. 2016). However, the question of *how* stress affects the auditory pathway to induce tinnitus remains open.

Non-auditory health conditions strongly associated with stress include depression and anxiety (Craske and Stein 2016; Michaelides and Zis 2019). Interestingly, tinnitus patients frequently report having depressive and anxious symptoms (Zöger et al. 2006; Adoga et al. 2008; Zirke et al. 2013; Gomaa et al. 2014; Salviati et al. 2014; Conrad et al. 2015; Waechter and Brännström 2015; Bruggemann et al. 2016; Brueggemann et al. 2019). Also, tinnitus patients are significantly more likely to have symptoms of depression and anxiety when compared to age-matched control subjects (Danioth et al. 2020) and a higher incidence of anxiety (26.1%) and depressive symptoms (25.6%) as compared to age-matched persons without tinnitus (9.2% incidence of anxiety and 9.1% of depressive symptoms) (Bhatt et al. 2017). In agreement, current epidemiological studies suggest a direct correlation between tinnitus and anxiety or depression (Hébert et al. 2012).

Definitive scientific evidence demonstrating that stress causes tinnitus is still lacking. There are multiple reasons for this knowledge gap, the main being the patients' diffuse knowledge about the time of onset of the phantom sound and a lack of medical and psychological information from that period. The other reason is that the persons who developed tinnitus may not necessarily be bothered by it. What is not lacking is the abundant clinical data demonstrating that the individuals affected by tinnitus are more likely to experience a higher level of stress than this experienced by tinnitus-free patients (Betz et al. 2017; Biehl et al. 2019; Mazurek et al. 2019). Accordingly, various therapeutic methods such as cognitive-behavioral therapy (CBT), mindfulness-based cognitive therapy (MBCT), mindfulness-based stress

reduction (MBSR), brief solution-focused therapy, narrative therapy, acceptance and commitment therapy (ACT), and eye movement desensitization and reprocessing (EMDR) have been used to reduce the tinnitus-induced burden (National Guideline 2020). The success of these types of therapeutic approaches in treating tinnitus points towards the essential role that stress plays in tinnitus pathobiology. However, the outstanding questions are *if* and *how* the stress-induced responses affect the auditory pathway to produce a sensory activation without an acoustic stimulus. Before an attempt to answer that question, the mechanism evoked by stress needs to be described.

2 Stressors

Two general types of stressors are recognized: psychological and physical stressors. Psychological stressors include mental stressors (concentration tasks, memory requirements, intelligence tests) (Kirschbaum et al. 1993), social stress situations, and stressors acting throughout life (posttraumatic stress disorder after deprivation or abuse), which produce changes in stress regulation patterns over a lifetime and induce a central hyper-responsiveness (Heim and Nemeroff 2009; Lupien et al. 2009; Slavich and Shields 2018). Environmental (physical) stressors include hypo- or hyperthermia, noise, over-illumination, or overcrowding.

The effects of some physical stressors – namely noise and temperature changes – were and still are studied extensively in the auditory system (Seifert et al. 1998; El Ganzoury et al. 2012; Sliwinska-Kowalska and Davis 2012; Lie et al. 2016; Le et al. 2017). Also, the effects of psychological stressors on the auditory system have been investigated, providing insights into the pathophysiology of tinnitus and hyperacusis (Horner 2003; Mazurek et al. 2010b; Hasson et al. 2013; Mazurek et al. 2015). Interestingly, tinnitus itself is considered to be a stressor.

3 Neurobiological Mechanisms Associated with Tinnitus Induction

Tinnitus is a symptom, and the conditions associating with tinnitus are discussed in detail elsewhere in this book. In this chapter, selected processes leading to tinnitus are listed, and later, their association with stress is demonstrated.

It is well accepted that tinnitus initiation is associated with damage to the auditory periphery, whereas tinnitus maintenance correlates with the progressive changes in the central auditory system (Eggermont 1990; Eggermont and Roberts 2015; Haider et al. 2018). The cochlear structures that could be damaged include outer and inner hair cells, supporting cells, and spiral ganglion neurons. On the molecular level, the injury can be induced by glutamate excitotoxicity (Puel et al. 2002; Ryan and

Bauer 2016; Kim et al. 2019), an excess of free radicals (Evans and Halliwell 1999; Huang et al. 2000; Rybak et al. 2019), and all processes leading to apoptosis (Op de Beeck et al. 2011; Gauvin et al. 2018). On the structural level, cochlear synaptopathy has been proposed to represent an important mechanism contributing to tinnitus onset (Liberman and Kujawa 2017; Altschuler et al. 2019). However, this mechanism has recently been questioned for humans (Guest et al. 2017) and animals (Pienkowski 2018).

Interestingly, accumulating evidence supports the view that the limbic system makes an essential contribution to the onset and maintenance of tinnitus percept (Jastreboff 1990; Lockwood et al. 1998; Mühlau et al. 2006; Landgrebe et al. 2009; Leaver et al. 2016; Ryan and Bauer 2016; Caspary and Llano 2017; Qu et al. 2019; Kapolowicz and Thompson 2020). The limbic system was proposed to provide negative feedback to the central auditory system and, thus, to turn off the perception of the tinnitus sound. However, the stress-affected limbic system no longer provides that negative feedback, leaving the phantom sound uncancelled (Rauschecker et al. 2010). Corroborating studies have demonstrated significant volume reduction of grey matter in the (left) parahippocampal cortex of tinnitus patients (Landgrebe et al. 2009; Besteher et al. 2019; Liu et al. 2019).

4 Stress-Induced Responses

The term *stress* has been in use for about a century. Physicists first introduced it in an attempt to describe a distribution of energy leading to tension. In the twenties of the last century, an American physiologist Walter Cannon used the term *stress* when describing *fight or flight* response (Cannon 1922). A few years later, a Hungarian-Canadian endocrinologist, Hans Seyle originated the research on emotional stress (Selye and Fortier 1949; Selye 1950). The experiments performed with animals led to the discovery of the hypothalamus-pituitary-adrenal axis (HPA axis) (Fortier and Selye 1949), which we will describe later in detail. He also introduced the concept of positive or negative stress and explored various states of stress reactions. The followers of Seyle's model of stress continue to conduct research trying to understand how the emotional status may influence the functioning of cells, tissues, and the entire organism, leading in some cases to somatic pathologies.

The factors inducing stress are termed *stressors* and can be divided into physical and psychological stressors. The physical stressors (such as pain, heat, or cold) can cause similar but not identical effects on the organism compared to emotional stressors (Hermann et al. 2019). Also, duration of stress is an essential factor, where the outcome of acute, short-time stress differs from the chronic exposure to stress (Bryant 2018). Therefore, the result of stress differs, depending on the type of stressor, age, gender, genetics, social status, and education of the affected person (Fig. 1) (Oyola and Handa 2017).

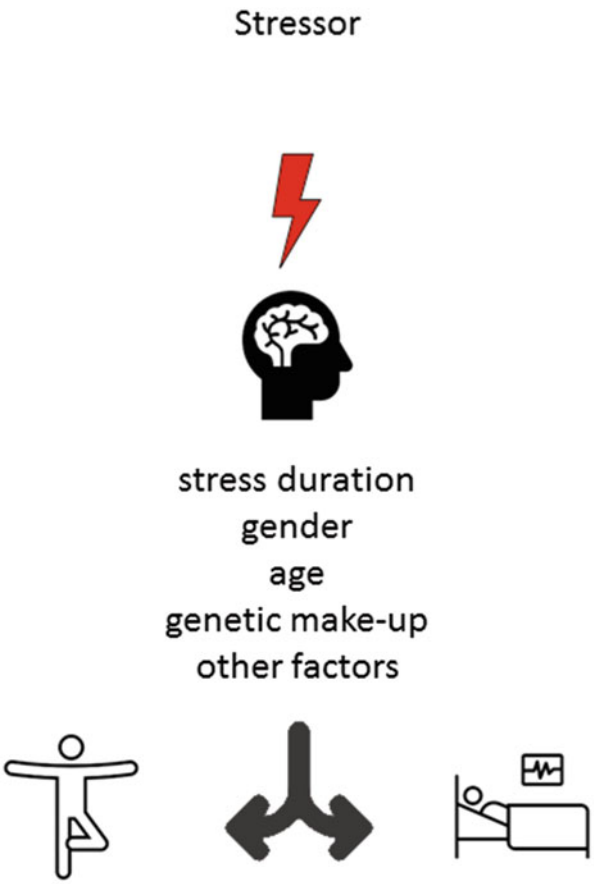

Fig. 1 Schematic illustration of the factors influencing the outcome of stress. The stressors involved in the stress event (physical, psychological, or both) induce effects, depending on age, gender, stress duration, and several other factors. The outcome of stress may range from staying healthy to acquiring a health condition

4.1 The Hypothalamus-Pituitary-Adrenal Axis (HPA Axis)

The pioneering work of Hans Seyle paved the way for understanding the somatic mechanisms induced by emotional stress (Selye 1937). The principal pathway caused by stress is the hypothalamic-pituitary-adrenal axis (HPA axis). HPA axis encompasses the following structural elements: the hypothalamus (paraventricular nucleus, PV), pituitary gland (the anterior lobe), and the adrenal cortex. The hypothalamic neurons in PV are capable of synthesizing vasopressin and corticotropin-releasing hormone (CRH). These two peptides are secreted upon stress and stimulate adrenocorticotropic hormone (ACTH) release from the pituitary gland. ACTH promotes the production and release of corticosteroids from the adrenal gland. The corticosteroids-driven negative feedback mechanism tightly regulates the HPA axis (Fig. 2). In humans, the principal corticosteroid produced is cortisol, whereas in rodents, it is corticosterone.

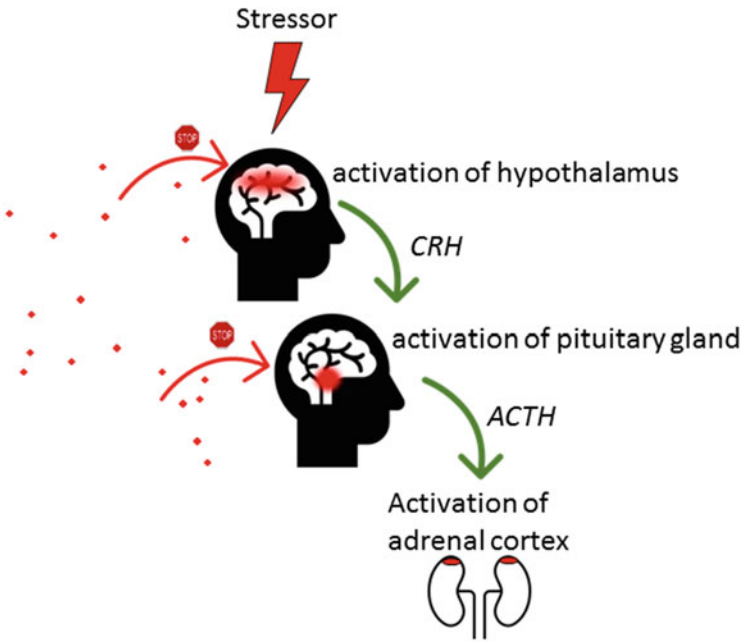

Fig. 2 The schematic HPA pathway. Upon stress, the CRH is released from the hypothalamus to activate the pituitary gland and induce adrenocorticotropic hormone (ACTH) release. In response to ACTH, the adrenal gland produces and releases glucocorticoid hormones, which in turn inhibit the production of ACTH and CRH. The green color indicates the stimulatory pathway, while the red color indicates the inhibitory pathway

In response to diurnal rhythm or stress, cortisol is released to the bloodstream to act on all tissues and cells of the body, influencing the metabolism and gene transcription regulation. The metabolic effect of cortisol is associated with the de novo production of glucose (gluconeogenesis) in the liver, kidney, intestine, muscle, and brain (Yip et al. 2016). In contrast, gene transcription regulation occurs almost in each somatic cell due to glucocorticoid receptors' ubiquitous presence (Fig. 3). The glucocorticoid-mediated transcriptional modulation is complex and comprises several types of processes involving direct binding of glucocorticoid-glucocorticoid receptor complex to specific sequences on the genomic DNA and activation/deactivation of several transcription factors through various mechanisms. Upon binding its receptor (GR) and translocation to the nucleus, GR inhibits or stimulates the expression of several genes – these genes belong to the so-called *glucocorticoid-responsive genes*. The glucocorticoid-
responsive gene pattern differs depending on the cell type. For instance, in adipocytes, corticosteroids bind to 8,848 sites on the genomic DNA to upregulate the expression of 421 and downregulate the expression of 198 genes (Yu et al. 2010). In contrast, only 4,392 sites are bound by corticosteroids in A549 epithelial cell line carcinoma (Reddy et al. 2009). Similarly, in the neuronal cell line PC12, a unique,

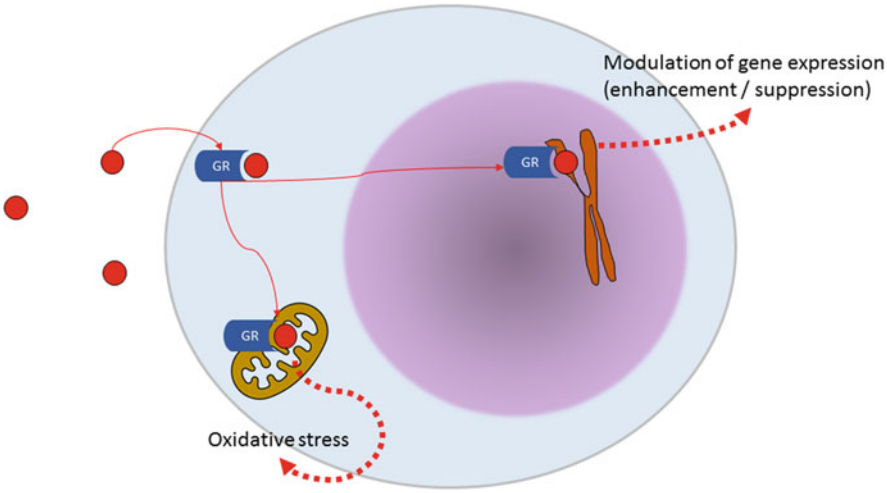

Fig. 3 The effect of corticosteroid on the cell on the molecular level. The corticosteroid attaches to the glucocorticoid receptor (GR) and translocates to the nucleus and the mitochondria, acting as a transcription factor. Upon binding to the chromosomal or mitochondrial DNA, GR influences gene transcription in both organelles, leading to altered transcription/translation (nucleus and mitochondria) and oxidative stress (mitochondria)

cell-type restricted GR specificity was described, demonstrating 1,183 genomic binding sites (Polman et al. 2012). The processes regulated by corticosteroids in the neuronal cells include neuron projection morphogenesis, neuron projection regeneration, synaptic transmission, and regulation of apoptosis, suggesting a strong influence of corticosteroids on neuronal plasticity.

The nuclear and mitochondrial DNA can be expressionally regulated by stress and glucocorticoids (Hunter et al. 2016), adding to the complexity of glucocorticoid effects in the cells, tissues, and entire body. Exposure to stress results in an inhibition of mitochondrial complex I activity and an increase in reactive oxygen species (ROS) production, damaging the affected cells (Fig. 3). The physiological significance of mitochondria affected by stress was demonstrated in the animal models of anxiety-related disorders and human anxiety disorders (Misiewicz et al. 2019).

Under ideal physiological circumstances, the HPA axis can be quickly activated by stress and promptly stopped by negative feedback via corticosteroids (cortisol in humans). However, under chronic stress, the inhibitory mechanisms are either no longer in place or aberrant. In response to experimental social stress (Trier Social Stress Task (Kirschbaum et al. 1993)), healthy subjects produce free cortisol detectable in saliva 30 min later (Hébert and Lupien 2007). Tinnitus patients were shown to have delayed reactions to the same stressor, suggesting anomalous HPA axis responses.

The potential effects of the HPA axis on the cochlea and its hypothetical contribution to the onset of tinnitus are discussed below.

4.2 *Potential Involvement of the Stress-Activated HPA Axis in Tinnitus Generation*

4.2.1 Mitochondrial Damage and ROS Formation

The association between mitochondrial DNA (mtDNA) integrity and cochlear physiology is clearly seen in the human genetically-mediated syndromic and non-syndromic deafness, caused by the mutations in mtDNA (Kokotas et al. 2007). Moreover, some of the isoforms and mutations in mitochondrial DNA have been associated with presbyacusis in humans and the mouse model and correlated with a loss of spiral ganglion neurons (Pickles 2004; Crawley and Keithley 2011). In addition, it was shown that some specific mutations in the mitochondrial DNA, which associate with tinnitus, are ethnically distributed (Mostafa et al. 2014; Lechowicz et al. 2018). Some other mutations in the mtDNA, which targeted the 12S rRNA gene known to predispose to ototoxicity, are also associated with a sudden tinnitus onset (Fischel-Ghodsian et al. 1997).

In the cochlea of humans and animals and the organ of Corti-derived cell line, ototoxic medications such as cisplatin or gentamicin were shown to induce overproduction of reactive oxygen species leading to mitochondrial damage and finally, hair cell death (Bertolaso et al. 2001; Poirrier et al. 2010; Sheth et al. 2017; Desa et al. 2018; O'reilly et al. 2019). Collectively, this evidence strongly implies the detrimental role of damaged mitochondria and the overproduction of reactive oxygen species in cochlear pathology. Even though no studies have examined the role of the HPA axis in the generation of ROS in the cochlea, this process might still play a role in the induction of cochlear hearing loss and tinnitus.

4.2.2 Glucocorticoid-Modified Expression of Genes

Glucocorticoid- (GR) and mineralocorticoid receptors (MR) are expressed in the cochlea by various cell types such as inner and outer hair cells, spiral ganglion cells, supporting cells (ten Cate et al. 1993; Zuo et al. 1995; Kil and Kalinec 2013). Stria vascularis expresses mainly MR, whereas fibrocytes type IV mainly GR (Kil and Kalinec 2013). In an animal model, the short-term acute restrain was used to study the effect of non-auditory stress on the auditory pathway. In the spiral ganglion neurons, the restrain has induced GR's nuclear translocation, whereas in the cochlea, it downregulated the expression of cochlear GR. The changes occurred 24 h after stress and indicated negative feedback mechanism (Tahera et al. 2006a). The GR translocation was associated with protection against noise-induced injury (Tahera et al. 2006b). In contrast to short-term stress, long-term stress was shown to be associated with an increased incidence of hearing loss and tinnitus in humans, indicating that the general dysregulation of the HPA axis might be detrimental to the auditory system (Canlon et al. 2013; Herr et al. 2018).

Many studies of gene expression in the cochlea following exposure to corticosteroid have been performed using synthetic steroid dexamethasone. These studies

demonstrated, for instance, that dexamethasone modulates the expression of genes encoding apoptosis-relevant proteins in the cochlea (Hoang et al. 2009). The somewhat limited evidence obtained using the stress model is consistent with cochlear gene expression being modulated during or after stress. However, only a few genes were investigated, of which hypoxia-inducible factor 1 (Hif1) was downregulated in the cochlea of Wistar rats 7 days after mild, 24-h-long stress (Mazurek et al. 2010a).

To summarize, the influence of stress released corticosteroids on gene transcription in the cochlea should be further studied using a global approach (e.g., mRNA sequencing) and with a large-scale data.

4.2.3 Influence of HPA Axis on Glutamate Signaling

The role of cochlear glutamate-depending signaling in the generation of tinnitus has been suggested (Puel et al. 2002; Sahley et al. 2013). The model has been supported by a study using C57BL/6J mice that provided evidence of an imbalance between cochlear NMDA and AMPA receptors during a long-term administration of salicylate, associated with the induction of tinnitus (Cui et al. 2019). Consistent with this observation, salicylate-induced tinnitus could be inhibited by selective NMDA blocker memantine (Ralli et al. 2014). In primary hippocampal cultures, corticosterone was shown to increase the endocytosis of AMPAR, leading to its surface decrease (Martin et al. 2009). It remains to be determined if the HPA axis influences overexpression of NMDA or downregulation of AMPA receptors in the cochlea, therefore contributing to cochlear synaptic plasticity and eventually to a generation of tinnitus.

Stress (e.g., forced swim stress and restraint stress) has been shown to increase glutamate release in the medial prefrontal cortex, hippocampus, striatum, and nucleus accumbens in rats (Moghaddam 1993). Moreover, corticosterone application on rats hippocampal brain slices rapidly increased the glutamate release via MR (Karst et al. 2005). Although this phenomenon has not yet been investigated in the cochlea, it was demonstrated that spiral ganglion neurons (Furuta et al. 1994) and the inner hair cells express MR (Yao and Rarey 1996), making the glucocorticoid-mediated rapid glutamate release in the cochlea hypothetically possible. Such a quick release of glutamate could stimulate the auditory pathway without acoustic stimuli. Also, depending on a local concentration of freshly released glutamate, it could lead to excitotoxicity associated with peripheral deafferentation and tinnitus (Sahley and Nodar 2001).

4.3 The Sympathetic-Adreno-Medullar (SAM) Axis

The sympathetic-adreno-medullar axis is one of two stress axes, which alongside the HPA axis acts as a mediator for specific stress responses and adaptation to psychological and environmental stressors. The SAM axis mediates quick responses that

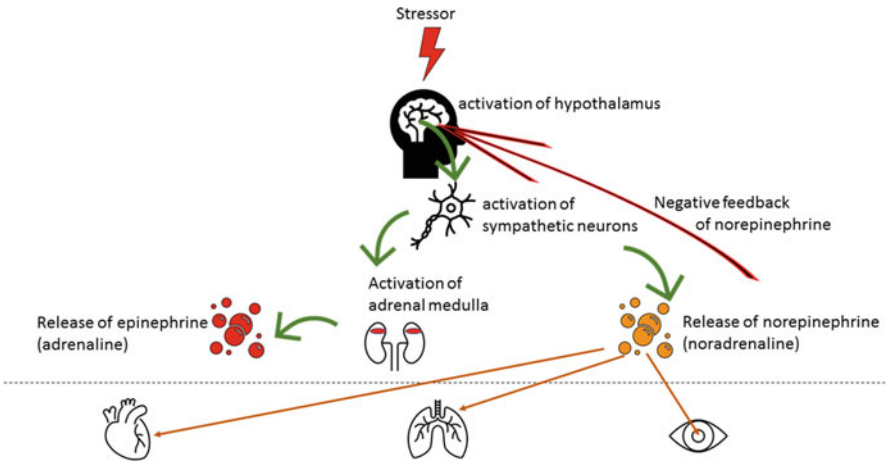

Fig. 4 The schematic presentation of the sympathetic-adreno-medullar (SAM) axis. Stress activates the hypothalamus, which in turn activates sympathetic neurons. The sympathetic neurons projecting to the adrenal medulla induce epinephrine (adrenaline) release into the bloodstream. Epinephrine increases the supply of glucose and oxygen to the brain and muscles (flight or fight) and suppresses the body's non-crisis functions (e.g., digestion). The sympathetic neurons themselves release the norepinephrine (noradrenaline) and, thus, activate all cells expressing adrenergic receptors. The effects of norepinephrine range from an increase in the blood volume pumped by the heart, expanding the respiratory pathway in the lungs, narrowing the blood vessels in non-essential organs, and pupil dilation

activate *fight or flight* reaction. During that reaction, several tissues and organs necessary for survival are activated (e.g., muscles, heart, and respiratory function), whereas tissues and organs with tasks that are non-essential for survival (e.g., digestion) are suppressed at the same time. The SAM axis comprises the hypothalamus, sympathetic neurons, and catecholamines (epinephrine and norepinephrine) (Fig. 4). Similar to the HPA axis, there is a negative feedback system mediated by epinephrine, which extinguishes the SAM activation.

4.4 Potential Involvement of the Stress-Activated SAM Axis in Tinnitus Generation

4.4.1 Arterial Hypertension

Arterial hypertension has often been considered a cause of tinnitus. This causative relationship's suggested mechanism is damage to cochlear microcirculation, induction of hearing loss, and deafferentation of the auditory periphery. Studies using

spontaneously hypertensive (SH) and wild-type rats demonstrated differences in age-related hearing loss between the two rat strains (Borg and Viberg 1987). A progressive loss of the outer hair cells was observed in the SH but not wild-type rats already at the age of 3 months. A threshold shift in the high frequencies (16 and 24 kHz) was seen in the 21-month-old SH but not in wild-type rats.

Interestingly, the study scrutinizing the effect of noise on the cochlear vascular system in the SH and wild-type rats demonstrated dramatic differences between the two types of animals and suggested hypertension-induced cochlear vascular damage (Axelsson et al. 1983). In addition to vascular damage, arterial hypertension negatively affected the endocochlear potential (Mosnier et al. 2001). In agreement with that, several clinical studies have reported an association between arterial hypertension, hearing loss, and tinnitus (Figueiredo et al. 2015; Yang et al. 2015; Figueiredo et al. 2016). Also, a study with 80 tinnitus patients and 80 tinnitus-free subjects demonstrated that the nighttime systolic and diastolic blood pressure of tinnitus patients is higher than in the age-matched control subjects (Değirmenci et al. 2014), suggesting possible continuous upregulation of SAM axis.

4.4.2 Catecholamines

Catecholamines released during activation of the SAM axis mediate their effects through various receptors. One of those receptors is a G-protein coupled α2-adrenergic receptor, mediating vascular smooth muscle reaction, inhibiting the norepinephrine release, and platelets' activation. The presence of α2-adrenergic receptors in cochlear microvasculature was verified in an animal model (gerbils), and α2-adrenergic stimulation provided experimental evidence for catecholamine-induced cochlear vasoconstriction (Carrasco et al. 1990). Moreover, vasoconstriction is associated with hypoxia or ischemia. In the inner ear, experimentally induced hypoxic and ischemic events lead to hair cell loss in an animal model (Shirane and Harrison 1987; Mazurek et al. 2003), followed by threshold shift (Sawada et al. 2001) and likely tinnitus. The expression of α2-adrenergic receptors was also demonstrated on the outer and inner hair cells and the supporting cells, the spiral ganglion neurons, stria vascularis, and all five types of fibrocytes in the cochleae of developing rats (Cai et al. 2013).

Brimonidine, an α2 adrenergic agonist (activator), protected the auditory hair cells from gentamicin-induced toxicity (Cortada et al. 2017). Surprisingly, inhibition of the α2a adrenergic receptor with istradefylline (α2 adrenergic antagonist) also protected the hair cells from glutamate excitotoxicity (Han et al. 2019). However, the above experiments were performed on an isolated organ of Corti and might not reflect the real-life situation, where the interplay of hypoxic/ischemic and toxic

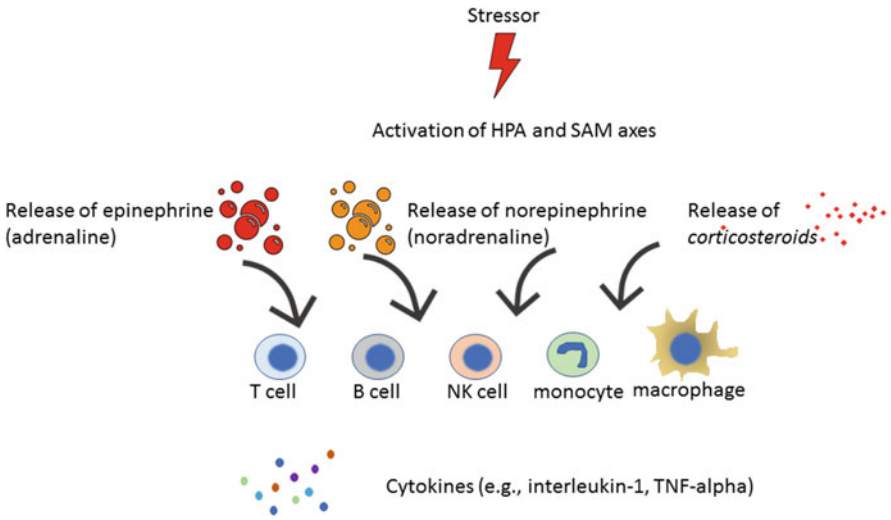

Fig. 5 Stress-induced immune axis

events and the protective mechanisms would yield an extrapolated role for α2-adrenergic receptors in the inner ear. Here too, more research should be performed to address the unanswered questions.

4.5 The Immune Axis

The immune system consists of specialized cells (neutrophils, eosinophils, basophils, lymphocytes, and monocytes) circulating in the blood, existing in primary lymphoid organs, or permanently residing in other tissues (e.g., resident macrophages). Under the steady-state condition, the immune system continually communicates with the endocrine and nervous systems, and there is a homeostatic balance between the three. During stress, the activation of the HPA and SAM axes leads to the release of mediators acting directly on the immune cells (Fig. 5), e.g., changing the number of circulating B cells (McGregor et al. 2016) or increasing the number of circulating T cells (Gupta et al. 2017). Also, chronic stress can change the activation status of immunocytes (Arranz et al. 2009) and modify cytokines' release (Jung et al. 2019).

The mediators set free by activation of the HPA and SAM axes (corticosteroids, norepinephrine, and epinephrine) act directly on the immune cells and modify their release from the primary lymphoid organs, affect their migration and alter the cytokine expression patterns.

4.6 Potential Involvement of the Stress-Activated Immune Axis in Tinnitus Generation

4.6.1 A Direct Influence of Stress on the Immune Cells in the Cochlea

Several types of immune cells have been found in a steady-state, healthy cochlea of humans and animals (Hu et al. 2018). The cochlear immunocytes include resident macrophages (Hu et al. 2018; Liu et al. 2018; Kishimoto et al. 2019), NK cells (Iguchi et al. 1997), and T cells (Liu and Rask-Andersen 2019). Of all the immune cell types, resident macrophages' cochlear function has been studied in the most detail. Macrophages phagocytose the damaged hair cells in Corti's organ, thus preventing cochlear inflammation and consecutive hearing loss (Hirose et al. 2017). In addition to phagocytic features, cochlear macrophages possess still not well-understood repair abilities that enable regeneration of ribbon synapses after noise exposure (Kaur et al. 2019). It is tempting to speculate that cochlear macrophages' activity might be impaired by the stress mediators, especially by corticosteroids. This impairment could be of a long duration during chronic stress and might result in reduced phagocytosis, migration, and a compromised spiral ganglion repair process upon acoustic injury. Macrophages also reside in the stria vascularis, where they regulate the cochlear intrastrial fluid–blood barrier. Here, long-term suppression of resident macrophages via stress hormones could result in modulation of endocochlear potential, which might induce hearing loss and tinnitus, similarly to what is observed during the aging process (Keithley 2020). Cochlear immunology is a rapidly developing field, and information is being published frequently, advancing our understanding of immune- and non-immune processes mediated by the cochlear immune cells.

4.6.2 Influence of Cytokines

Cytokines released by the immune and non-immune cells, such as interleukin 1-beta (IL-1beta), IL-6, and TNF-alpha, were shown to influence the plasticity in the brain and the peripheral nervous system (Aldskogius and Kozlova 1998; Levin and Godukhin 2017). The influence of the cytokines on the synaptic strength, plasticity, and integrity varies depending on the co-signaling molecules, the presence of other cells, and many other factors. Cytokines can act directly on neurons and different cell types (e.g., cochlear immunocytes), and the outcome ranges between cochlear regeneration and cell death (Barald et al. 2018). Studies using an animal model of noise-induced hearing loss (NIHL) indicated that NIHL induced the expression of proinflammatory cytokine tumor necrosis factor-alpha (TNF-alpha) in the cochlea (Frye et al. 2019) and was associated with the development of tinnitus (Wang et al. 2019) and that pharmacological intervention or using genetically modified mice prevented this detrimental development. Further, in an animal model of salicylate-induced tinnitus, increased expression of genes encoding TNF-alpha and IL-1-beta

was observed in the cochlea and correlated with behaviorally tested tinnitus (Hwang et al. 2011). In a sample of 30 patients with chronic tinnitus, a correlation was found between TNF-alpha in serum and tinnitus loudness, total perceived stress, tension, and depression (Szczepek et al. 2014). Another study investigating tinnitus in the elderly noted a negative association between IL-10 and tinnitus loudness and duration (Haider et al. 2020). It remains to be clarified if cytokines' systemic concentration reflects that in the cochlea and how aging, inflammation, and infections may affect this balance.

5 Summary and Conclusions

Tinnitus is a symptom that may arise as a result of various changes in the auditory system. Persons with disturbing tinnitus perceive it as an unpleasant, distressing signal that negatively affects life quality, associates with anxiety and depression, and may last a lifetime. The accepted view on the primary mechanism inducing tinnitus is that it is a consequence of a cochlear lesion, which could have been caused by noise, ototoxic medications, the physiological aging process, or other means. Here, the evidence was reviewed for the emotional stress-induced mechanisms, which could contribute to cochlear pathologies and, in consequence, to tinnitus (Fig. 6). These mechanisms involve HPA axis-induced corticosteroid action on MR and GR, possibly leading to glutamate excitotoxicity and altered gene expression in the cochlea. The immune axis of stress can also be affected by the HPA axis, leading to modulation of the resident cochlear macrophages' function. Lastly, corticosteroids released upon HPA activation could contribute to the NMDA/AMPA disbalance.

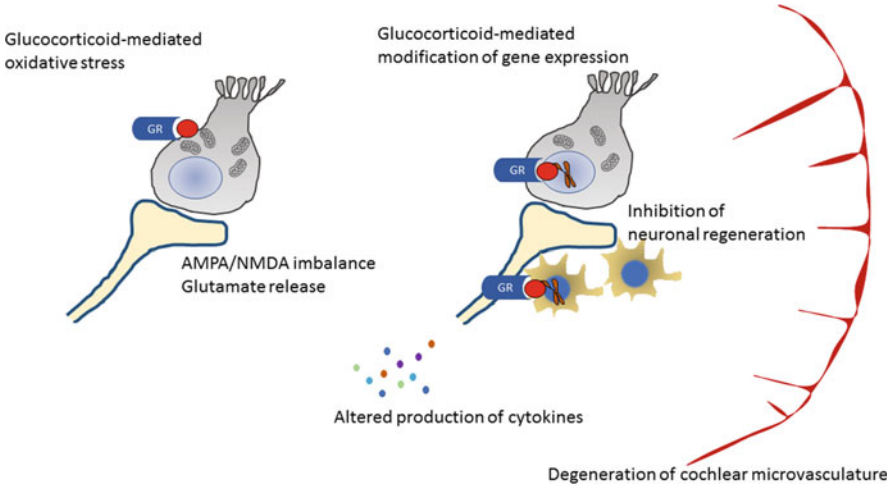

Fig. 6 Hypothetical model of some of the stress-induced events that could lead to cochlear pathologies and tinnitus

The SAM axis might increase blood pressure that induces degenerative changes in the cochlear microvasculature and changes in the organism's immune cells' repertoires, affecting cochlear immune cells.

Furthermore, SAM-induced vasoconstriction in the cochlea might likely cause hypoxia/ischemia, detrimental to the auditory hair cells and spiral ganglion neurons. It is concluded that all of the presented mechanisms need to be further investigated in the animal or ex vivo models. It is recommended for clinical practitioners to collect information about stressful events or chronic stress preceding the tinnitus onset. Furthermore, knowing the vital signs could add information to the stress-related status of a patient. Finally, taking into account that tinnitus itself acts as a stressor, the implementation of anti-stress therapies for tinnitus treatment is recommended.

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