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Stress and tinnitus

Introduction

What is emotional stress?

In psychology and biology, emotional stress is defined as an organism's response to environmental challenges. This response involves activation of the hypothalamic–pituitary–adrenal (HPA) axis, with systemic release of cortisol and adrenaline (epinephrine). Adrenaline stimulates the sympathetic nervous system and reduces the activity of the parasympathetic nervous system, whereas cortisol induces gluconeogenesis as well as lipolysis and proteolysis. The concerted action of adrenaline and cortisol results in sweating, increased blood pressure, increased heart rate, and increased blood sugar—all of them augmenting the organism's energy supply (**Fig. 1**). The stress responses are generally positive, that is, they lead to adaptation or to escape from a new, unknown situation (the so-called fight-or-flight response [1]). The adaptation process on a molecular level is mediated by cortisol-induced changes in the central nervous system (CNS; amygdala, hippocampus, and prefrontal cortex) via glucocorticoid and mineralocorticoid receptors. When persistent, this situation can lead to negative consequences, such as decreased neurogenesis, neuronal atrophy, and death. Some of the interesting but less understood responses to stress involve temporary difficulties with speech recognition [2] and general difficulties with sound processing, especially sound duration [3]. Persistent or repetitive stress may have major health consequences for the affected individual.

Stress can affect homeostasis of the organism

All biological systems struggle to keep their specific equilibrium, also called *homeostasis*, under all possible circumstances. In general, momentary deregulation of homeostasis can be quickly compensated and the system is brought back to balance. However, long-term deregulation of homeostasis can have harmful consequences for the organism. Stress can affect the homeostasis of various organs, which normally regain balance in a process of *allostasis*, leading to adaptation. However, prolonged stress may cause maladaptation, which is also called *allostatic load* (**Fig. 2**). Allostatic load is known to contribute to the worsening of or to de novo occurrence of conditions such as asthma [4], cardiovascular diseases [5], skin diseases [6], cancer [7], and many more. The possible contribution of allostatic load to the pathogenesis of tinnitus has been suggested but it still remains to be experimentally and clinically determined [8].

In this review, we present the latest views and perspectives on how emotional stress can influence the functioning and homeostasis of an organism in general and of the auditory system in particular, with an emphasis on tinnitus.

Molecular aspects of stress

Cortisol: a stress hormone with multiple actions

Emotional stress activates the HPA axis (**Fig. 1**) and is typically associated with an increased concentration of circulating systemic glucocorticoids—in humans, *cortisol*. *Cortisol* is a steroid hormone produced from cholesterol and released in response to stress or low glucose concentration in the blood. It stimulates gluconeogenesis and activates antistress and anti-inflammatory pathways. On a cellular level, cortisol induces two types of responses: rapid (nongenomic) [9] and slow (genomic) [10] responses. Rapid responses depend on cell signaling pathways, such as activation of protein kinase C (PKC) [11]. Slow responses depend on cortisol acting as a transcription factor inducing suppression or activation of gene transcription. The well-known gene targets of cortisol include, but are not limited to, the inflammatory cytokines, such as interleukin-1 (IL-1), IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-11, IL-13, or tumor necrosis factor (TNF)-α [12], explaining the anti-inflammatory mechanism of cortisol and glucocorticoids-based medications.

Emotional stress was demonstrated to affect gene transcription via overproduction of cortisol, which binds to glucocorticoid and mineralocorticoid receptors and acts as a transcription factor. The groups of target genes that can be directly regulated by glucocorticoids during stress include cell adhesion molecules, cell signaling molecules, transcriptions factors, and many others [10].

Genetic predisposition to stress

Serotonin transporter gene promoter 5-HTTLPR

To date, a link between tinnitus and genetic mutation remains unknown. However, there is a correlation between stress-induced disorders, such anxiety or depression, and tinnitus. In fact, patients affected by high-grade tinnitus usually have multi-

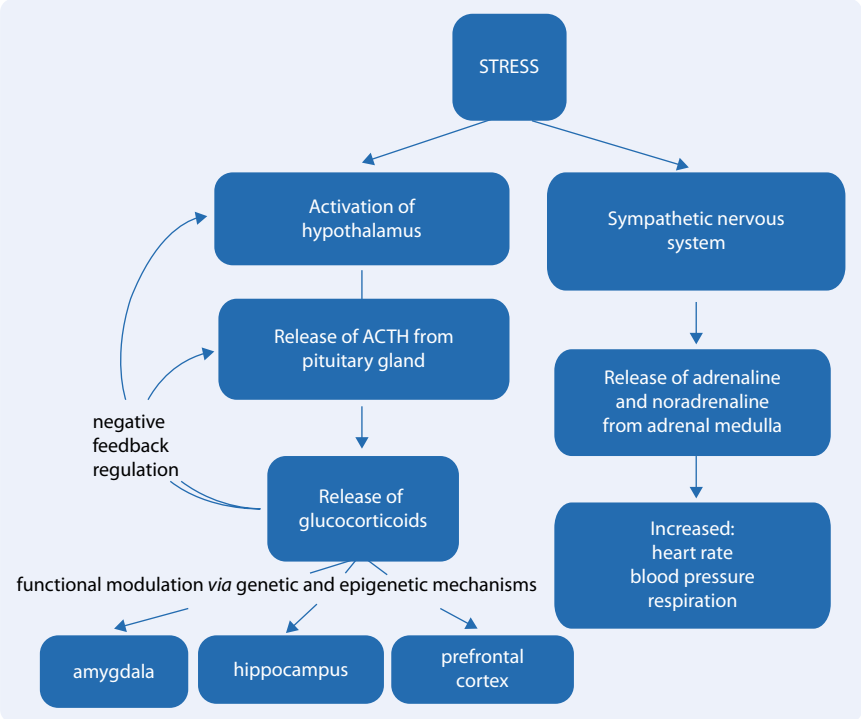

Fig. 1 ▲ Stress response mediated by the hypothalamic–pituitary–adrenal (HPA) axis. Stress can induce nerve cells in the hypothalamus to produce and release corticotropin-releasing hormone (CRH). CRH is also transported to the pituitary gland and induces production and release of adrenocorticotropic hormone (*ATCH*). ACTH stimulates cells of the adrenal glands to produce and release glucocorticoids (in humans, cortisol). High levels of cortisol inhibit the pituitary gland and hypothalamus (negative feedback loop). Cortisol can functionally modify the physiology of neurons in the amygdala, hippocampus, and prefrontal cortex. Stress can also activate the sympathetic nervous system via release of adrenaline and noradrenaline from the adrenal medulla, resulting in increased heart rate, blood pressure, and respiration

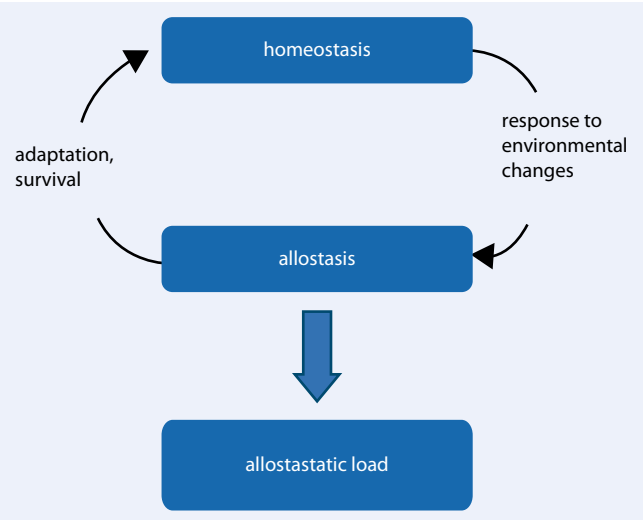

Fig. 2 ▲ The concept of homeostasis, allostasis, and allostatic load. The normal, physiological state of an organism (homeostasis) can be changed in response to environmental challenge (stress). The changed status is then called *allostasis*. Allostasis induces adaptation of an organism to the new situation, increases probability of survival, and helps to achieve *homeostasis*. When the allostasis status persists because of chronic or consecutively repeated stress, then the adaptation is not achieved and the organism's status changes to *allostatic load*. The allostatic load correlates with various conditions such as cardiovascular disease or depressive illness

ple comorbid conditions [13, 14]. For one of these conditions—depression—some of the genetic associations have been established and involve serotonin transporter gene polymorphism. There are two known alleles of the serotonin transporter gene promoter 5-HTTLPR: long (L) and short (S). Carriers of the short allele (SS) 5-HTTLPR are at risk of major depressive disorder (MDD) and major depression in response to stressful life events [15]. 5-HTTLPR polymorphism was not associated with the risk of tinnitus. However, tinnitus patients with the (LL) variant of 5-HTTLPR assessed their insomnia, difficulties with concentration, and the severity of tinnitus as more disturbing than the patients with (LS) or (SS) allele did [16]. Larger studies and work using animal models are necessary to provide unequivocal answers in this interesting filed.

Glucocorticoid receptor gene NR3C1

The gene encoding NR3C1 has several splice variants. The first level of genomic regulation of NR3C1 action happens on the splicing level (exon 9) that generates two main receptor variants: GRα and GRβ. GRα is capable of binding corticosteroids whereas GRβ is not, and is thought to be a negative regulator of GRβ. Another regulatory level is created by several polymorphisms in the NR3C1 gene associated with changes in glucocorticoid sensitivity. For instance, the substitution of Asn363 with serine (rs6195) correlates with clinically relevant augmented glucocorticoid sensitivity and an increased body mass index as well as with various mental conditions [17]. An opposite type of polymorphism that is associated with reduced glucocorticoid sensitivity includes the ER22/23EK (rs6189 and rs6190) and 9β (rs6198). Carriers of this polymorphism have lower blood low-density lipoprotein (LDL) cholesterol concentration and increased muscle mass and strength; they also live longer. A recent study demonstrated impaired auditory attention and auditory working memory in patients with Cushing syndrome who had the NR3C1 polymorphism [18].

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Abstract

Emotional stress is a constant companion of tinnitus patients, since this phantom sound can unfortunately be a very effective stressor. However, the mechanism of stress contribution to the onset or progression of tinnitus remains unknown. Here, we review the pathways induced by emotional stress and the outcome of their induction: corticosteroid-dependent changes in gene expression, epigenetic modulations, and impact of stress on neuronal plasticity and neurotransmission. Using clinical examples, we demonstrate the presence of emotional stress among tinnitus patients and we present methods to measure the degree of stress. The evidence causally linking emotional stress with tinnitus is still indirect—the main difficulty lies in the inaccessibility of human auditory tissues and the inability to directly measure tinnitus-induced psychological distress in animal models. However, we believe that translational research is the future way of filling this gap, finding the answers, and thereby improving both the diagnosis and treatment of tinnitus patients.

Keywords

Emotional stress · Tinnitus · Translational research · Homeostasis · Auditory system

Stress und Tinnitus

Zusammenfassung

Emotionaler Stress ist ein wesentliches Begleitsymptom von Tinnituspatienten, da dieser Phantomton oder dieses Phantomgeräusch ein direkter effektiver Stressfaktor sein kann. Der Mechanismus – Stress –, der zur Entstehung oder Progression von Tinnitus beiträgt, ist jedoch bis jetzt nicht komplett aufgeklärt. Die durch emotionalen Stress induzierten Signalwege und deren Folgen sind: kortikosteroidabhängige Veränderungen in der Genexpression, epigenetische Modulationen, Auswirkungen auf die neuronale Plastizität und Neurotransmission. Anhand klinischer Beispiele ließ sich das Vorliegen von emotionalem Stress bei Tinnituspatienten zeigen. In diesem Zusammenhang sind besonders Methoden zur Messung des Stressgrads im diagnostischen Setting sehr wichtig. Kausale Beweise, die emotionalen Stress mit Tinnitus verknüpfen, sind weiterhin indirekt – die Hauptschwierigkeit liegt zum einen im fehlenden Zugang zum menschlichen auditorischen Gewebe und zum anderen in der mangelnden direkten Übertragbarkeit der Grundlagenaspekte aus der tierexperimentellen Forschung auf den Menschen. Gerade deshalb ist die translationale Forschung der zukünftige Weg, um diese Wissenslücke zu schließen und Antworten zu finden sowie damit letztendlich Diagnostik und Behandlung von Tinnituspatienten auch im Hinblick auf die Stressexposition zu verbessern.

Schlüsselwörter

Emotionaler Stress · Tinnitus · Translationale Forschung · Homöostase · Auditorisches System

γ-Aminobutyric acid

The stress-induced HPA axis can be hampered by γ-aminobutyric acid (GABA)—the main inhibitory neurotransmitter. A single C/T nucleotide polymorphism (SNAP) in the 5' untranslated region of the $GABA_A$ receptor gene was shown to be associated with a higher basal cortisol concentration. Also, experimental social stress-induced cortisol production was greater in the carriers of this particular SNAP [19]. GABA receptors have been strongly implicated in the pathogenesis and treatment of tinnitus [20], but as direct players rather than connected with regulation of the HPA axis. Nevertheless, one should not exclude the possibility of GABA-related genetic alterations not only contributing to the decreased auditory function but also to HPA inhibition.

Epigenetics

Epigenetics is a discipline that studies changes in gene expression that are not caused by changes in the DNA sequence. The process of gene expression is an elementary process to maintain the life of any organism. Gene expression is regulated in a very controlled manner on a variety of levels:

- The DNA sequence itself
- The type and nuclear presence of transcription factors that induce or suppress gene expression
- The availability of enzymes and nucleotides necessary to perform transcription
- The accessibility of chromosomal DNA

Nuclear DNA is tightly packed as chromatin: This saves space and allows control over what is expressed and what is not. Such packaging is possible thanks to nuclear proteins called *histones*. Histones work like hair rollers, with the DNA wrapped around them. The histone/DNA wrap prevents the genes from being accessed by transcription factors and enzymes needed for gene transcription. However, this access can be regained upon posttranscriptional modifications of histones, by changing their three-dimensional structure and, therefore, DNA-binding properties. Changes in histone structure can be obtained by methylation, citrullination, acetylation, phosphorylation, SUMOylation, ubiquitination, or ADP-ribosylation. The best researched mechanisms of histone modification are the process of histone acetylation and deacetylation—both belonging to the key mechanisms of epigenetics. The physical status not only of histones but also of DNA influences the process of transcription. The main type of DNA modulation occurs via the addition of a methyl group by DNA methyltransferase.

Epigenetics, stress, and prenatal experience

Research regarding epigenetics and stress is on the rise. Recent basic research studies demonstrated that the mechanisms involved in the auditory Pavlovian fear conditioning and formation of posttraumatic stress disorder (PTSD) require general changes in histone acetylation and in DNA methylation, supporting the significance of epigenetic processes in conditions that are related to tinnitus [21]. Furthermore, clinical studies on the methylation status of the glucocorticoid receptor gene (NR3C1) promoter region of veter-

ans demonstrated hypomethylation of the promoter in individuals who were in combat and later developed PTSD, but not in those who were in combat and remained healthy [22].

Interestingly, numerous clinical studies have demonstrated that maternal mood during pregnancy also influences the methylation status of the glucocorticoid receptor gene (NR3C1) promoter region of a child, resulting in lower birth weight, childhood behavioral disorders, and changes in the brain structure [23]. In addition, the results of an animal study suggest that prenatally stressed rats suffer from hearing loss in adulthood [24] but in another, later, study the authors obtained contradictory results [25], leaving this interesting issue open for further research. In other works, where synthetic corticosteroids were used on dams during gestation, the authors confirmed the clinical findings of lower-birth-weight pups; in addition, in the 24-day-old offspring they found increased hearing thresholds and increased latencies during measurement of the auditory brainstem response (ABR), implicating corticosterone-induced hearing loss [26]. The mechanism of action was attributed to the decreased production of brain-derived neurotrophic factor (BDNF) [27], but it remains to be established whether epigenetic regulation is involved in this type of hearing loss.

Epigenetics and auditory conditions

How could epigenetic changes contribute to auditory pathologies? In the auditory system, changes in histone acetylation have been demonstrated to be essential for aminoglycoside-induced auditory hair cell loss. Addition of kanamycin, an aminoglycoside antibiotic that induces sensorineural hearing loss, was shown to correlate with histone deacetylation in the inner ear cells. In addition, the use of histone deacetylase inhibitors protected from kanamycin-induced auditory hair cell loss [28]. Moreover, a recent study suggested that disruption of the methylation process mediated by DNA methyltransferase I contributes to human hereditary sensory and neuronal neuropathies [29]. Epigenetic processes have recently been proposed as major mechanisms behind hearing loss-related syndromes and tumors [30], thus, possibly contributing to the pathogenesis of tinnitus. To date, little is known about the epigenetic mechanisms of gene regulation by stress in auditory conditions.

Stress, neuroplasticity, and tinnitus

One of the known cellular effects of stress involves *changes in neuroplasticity.* The phenomenon of neuronal plasticity is of utmost importance for development and learning, as it enables adaptation. *Neuroplasticity* is a general term that describes changes in synaptic and nonsynaptic plasticity. Interestingly, synaptic plasticity affecting the glutamate postsynaptic system and especially *the AMPA and NMDA receptors* (present in learning, memory, pain, and in the auditory pathways) was demonstrated to be regulated by stress [31, 32]. We have recently discussed the potential impact of stress on glutamate-related neuroplasticity in the auditory system [8]. Stress connected with learning or exercise positively affects neuroplasticity by enhancing the formation of new synapses and by augmenting neurogenesis [33], whereas chronic stress may influence the same processes in an opposite, negative way, contributing to conditions such as PTSD [34].

The mechanism behind nonsynaptic plasticity involves neurogenesis and, therefore, the most ubiquitous neuronal growth factor—BDNF. The expression of BDNF can be regulated in genetic and epigenetic ways, the latter being strongly stress-dependent [30].

Interestingly, neuroplasticity was shown to play a central role in the pathogenesis of tinnitus [35, 36]. An open question is whether the type of plasticity occurring in the auditory system during the onset and progression of tinnitus can be induced by stress-related phenomena.

Influence of stress on circadian rhythm

The circadian rhythm is an endogenously generated rhythm that regulates the organism's activity over a period of roughly 24 h. This process is tightly controlled by the so-called circadian clock regulated by daylight. Circadian rhythms are a property of all living organisms—from bacteria to humans.

The *Clock* gene (circadian locomotor output cycles kaput) encodes a transcription factor and histone deacetylase CLOCK, which is essential in the regulation of the circadian rhythm. CLOCK promotes transcription of other circadian genes and also acts on an epigenetic level by exhibiting histone deacetylase activity.

The daylight-induced activity of CLOCK in the CNS sensitizes neurons to adrenocorticotropic hormone (ACTH), which enhances the release of cortisol. In addition, upon hyperphosphorylation and translocation of CLOCK to the nucleus, it forms a dimer with the other circadian transcription factor BMAL1. This dimer binds the promoter sequence of *period* (per) and *timeless* (tim) and induces their transcription. *Period* is essential for the sleep phase whereas *timeless* is involved in cell cycle regulation [37]. The stress system communicates with the clock system through the HPA axis. Therefore, any stress-mediated deregulation of this system or allostatic load may lead to pathologies such as insomnia, mood conditions, or metabolic disorders [37].

Recently, the presence of CLOCK in the inner ear was identified by Barbara Canlon and her group at Karolinska Institute. The Clock system was shown to be essential for the protection of the peripheral auditory system from noise [38]. This discovery points to the fact that the disruption of circadian rhythm by stress can potentially lead to auditory pathologies known to be strongly associated with tinnitus.

Animal models in stress and auditory research

The animal models used in stress research involve mainly rats and mice, with a great preference for the latter, mainly because of the endless possibilities of genetic manipulations and a well-known genome. By contrast, auditory researchers traditionally used cats, guinea pigs, and gerbils in their experiments. In recent years, mice and rats have also started to be used more readily by auditory scientists, one of the purposes being for tinnitus research.

The stress models engage physical and psychosocial types of stress. Physical stress comprises electrical shock, restrain stress, tail stress, and cold water stress, whereas psychosocial stress involves separation, overcrowding, or exposure to a predator's scent [39]. The models used in tinnitus research often require the behavioral training of animals to react in a specific way to the sound of tinnitus [40]. Combining the two—stress and tinnitus models—is already in progress in various laboratories [8, 41, 42] and should in the near future deliver vital answers to the main question: Can tinnitus be directly induced by stress?

Stress in tinnitus

Stress is sometimes reported as an etiology of tinnitus [43, 44], and in the clinic, tinnitus individuals often complain that their tinnitus is "louder" during stressful periods [45]. For instance, of 125 individuals with tinnitus who participated in research, 53.6% reported that their tinnitus had appeared during a stressful life period and all but two individuals could name a specific event such as the death of a loved one, divorce, or job loss, suggesting that exposure to stress triggered tinnitus (unpublished data, S. Hebert). Moreover, 52.8% reported that their tinnitus increased during stressful periods. Individuals who reported both constituted 34.4% of the sample and those who reported neither were only 16%. Thus, there seems to be a commonly accepted association between stress and tinnitus, yet empirical evidence is still scarce. As underlined accurately by Canlon and colleagues in a recent review [46], the word *stress* is used to designate both an external exposure and internal response, and therefore can lead to confusion. Can stress as an external exposure trigger tinnitus, or is it that stress is an internal response, or consequence, to having tinnitus? Before discussing a potential causal relationship between tinnitus and stress, we will review some of the evidence showing an association between stress and tinnitus.

Several studies have demonstrated an association between stress and tinnitus, either by examining psychometric instruments (questionnaires), physiological responses to stress tasks, or by measuring the levels of stress hormones.

Association between tinnitus and stress measured by questionnaires

Studies that have used stress questionnaires have found a higher prevalence of self-reported stress levels in tinnitus patient samples. Using the Depression, Anxiety, and Stress Scale (DASS), which is sensitive to levels of nonspecific arousal, Gomaa and colleagues [47] reported that among 100 individuals with tinnitus, only 25 had normal stress levels. The majority had at least mild-to-moderate (N=44) or severe-to-extreme (N=31) stress levels. By contrast, none of the 46 patients with hearing loss but no tinnitus suffered from stress. A similar finding was reported by Zirke and colleagues [48]. When comparing the prevalence and severity of psychological comorbidity using the Perceived Stress Questionnaire (PSQ) in 300 tinnitus patients with patients with other chronic illnesses, namely, chronic pain, chronic asthma, and atopic dermatitis, patients with tinnitus had a lower comorbidity rate compared with those who had chronic pain, asthma, or atopic dermatitis. However, when the tinnitus group was split into compensated (defined as annoyance only in quiet and under stress) and decompensated (defined as permanent annoyance) tinnitus subgroups, decompensated tinnitus patients had more psychological disorders than compensated tinnitus patients (77% vs. 39.5%). Also, decompensated tinnitus was accompanied by higher frequencies of affective disorders (39% vs. 17.5%) and neurotic, stress-related, and somatoform disorders (36% vs. 21%). In both studies there was a significant correlation between stress scores and tinnitus severity.

Association between tinnitus and stress measured by physiological responses to stress tasks

Psychological stress as measured psychometrically has been difficult to correlate with physiological stress levels. Weise and colleagues [49] investigated whether tinnitus patients show increased physiological levels of arousal, more intense stress reactivity patterns, and exaggerated psychological strain compared with healthy controls. Seventy tinnitus patients and 55 healthy controls were exposed to various stress tests such as noise and arithmetic while muscular reactivity, peripheral arousal, and strain ratings were assessed. Tinnitus patients reported significantly more strain during stress tests compared with healthy controls; however, despite a trend toward more activation in tinnitus, few physiological reactivity patterns differed significantly between the two groups. Strain reports and physiological data were only marginally correlated.

In a further study the same group [50] examined psychological and physiological reactivity of tinnitus patients before and after a treatment program that included a combination of cognitive-behavioral therapy and a psycho-physiological treatment using a biofeedback approach. Overall, tinnitus patients showed a significant reduction of muscular activity but, again, these effects were unrelated to psychological ones.

Association between tinnitus and stress measured by cortisol and other stress hormones levels

A few studies have used the stress hormone cortisol as an objective measure of stress. As mentioned earlier, cortisol is the end product of a cascade of hormone secretions called the hypothalamic–pituitary–adrenal (HPA) axis. Cortisol secretion may be measured on a diurnal basis (e.g., basal) or in acute stressful situations (e.g., responsive). Basal cortisol secretion protects and regulates vital functions and is mediated by mineralocorticoid receptors (MRs). Responsive cortisol secretion during acute stress serves for energy mobilization and is mediated by glucocorticoid receptors (GRs). When a stressor is detected, the hypothalamus secretes the releasing factor captured by the pituitary gland, which releases ACTH; this itself is captured by the adrenal cortex, which in turn secretes cortisol. An autoregulation then follows by way of feedback loops that function somewhat like a thermostat. Besides this closed-loop functioning, the HPA axis also functions as an open loop driven by the CNS. Areas of the brain such as the amygdala, hippocampus, and hypothalamus stimulate and inhibit the HPA axis to different degrees depending on the

time of day, season, and physical or environmental stressor.

Measuring basal cortisol and other stress-related hormone secretion in a large group of 344 tinnitus patients and 89 healthy people without tinnitus, Kim and colleagues [51] found a higher proportion of tinnitus patients with abnormally high levels of stress-related hormones norepinephrine (NE) and 5-HIAA (a metabolite of serotonin). However, cortisol levels did not differ between groups. This is hardly a surprising finding since there was a single cortisol sample per patient, which is insufficient for an appropriate estimate of the diurnal secretion. In addition, cortisol is highly prone to variations due to common uncontrolled diseases such as uncontrolled diabetes and hypertension, sleep medication, and so on. Therefore, stringent inclusion and exclusion criteria must be applied especially when older patients are involved.

One study on basal cortisol applying appropriate selection criteria showed no difference between tinnitus and a control group without tinnitus when considering raw cortisol levels over five measurement times averaged over 3 days [52]. However, when the tinnitus group was split into high- and low-distress tinnitus subgroups based on responses to a questionnaire, the tinnitus with high distress group had overall higher basal cortisol levels than the low-distress group and controls. This finding is similar to the ones reported for depression. However, a further study examining the acute stress response reported surprising findings [53]. Participants underwent a stressful task, the Trier Social Stress Test, which consists in a 10-min preparation time followed by 10-min free speech and mental arithmetic task. With a normally functional HPA axis, there is a peak cortisol secretion around 20–30 min after stress anticipation and then recovery to prestress levels. Indeed, the control group without tinnitus displayed this pattern. By contrast, the tinnitus group had a much lower and delayed cortisol secretion, despite psychological stress levels similar to controls. Of note, however, tinnitus intensity as measured on a 10-point Likert scale did not show any variation throughout the task. The blunted stress response of the tinnitus group was similar to that of patients with chronic fatigue syndrome, suggesting an exhausted stress response due to long-term stress in tinnitus participants. The apparent contradiction between these two studies could be explained by the fact that basal cortisol levels and acute stress response are modulated by two distinct feedback systems, mineralocorticoids receptors (MRs) and glucocorticoid receptors (GRs), respectively, or by the fact that in the basal cortisol study tinnitus duration was shorter (7.2 years on average) than in the acute stress study (14.7 years on average). A possibility is that after a period with increased basal cortisol, the chronic arousal of the HPA axis leads to an exhaustion phase.

The hypothesis of HPA axis exhaustion in tinnitus was further tested using the low-dose dexamethasone suppression test (DST) [54]. Dexamethasone is a synthetic cortisol with high affinity to GRs (responsive stress) rather than MRs (basal cortisol). The low-dose DST indicates the sensitivity of the negative feedback response of the HPA axis to glucocorticoids by selectively activating the pituitary GRs. Cortisol hypersuppression after low-dose DST challenge reflects HPA-axis exhaustion and has been reported in patients with PTSD, whereas cortisol nonsuppression reflects HPA-axis hyperactivity and has been reported in depressed patients. The tinnitus group showed an almost complete cortisol suppression (i.e., a hypersuppression) compared with controls without tinnitus, thus supporting the HPA-axis exhaustion hypothesis. Interestingly, decreased hearing discomfort levels were also associated with cortisol hypersuppression, only in the tinnitus group. This finding is consistent with the study of Hasson and colleagues [55], in which they reported a decrease in discomfort loudness levels in women with high levels of burnout after they had been submitted to acute stress.

Stress-oriented therapeutic interventions

Stress-oriented therapeutic interventions are an effective tool in tinnitus therapy. Such interventions can be of short or long duration. Short-term stress-oriented interventions include relaxation techniques, de-focusing of auditory attention from tinnitus percept, or autosuggestion. Long-term interventions include relaxation exercises, time management, problem solving, and change of attitude, positive experiences, and interpersonal contacts.

Pharmacological stress-oriented tinnitus interventions could in the future involve histone deacetylase (HDAC) inhibitors to counteract the long-term epigenetic effects of stress as well as BDNF-based therapy to promote neurogenesis and regenerative neuroplasticity in the auditory and limbic systems of tinnitus patients.

Summary

In conclusion, clinical studies show that tinnitus is associated with significant HPA-axis dysregulation as found in other stress-related diseases. Conceivably, basal cortisol levels are first increased and because of chronic stress are followed by an increased sensitivity to negative feedback, eventually resulting in a blunted acute stress response and HPA-axis exhaustion. Besides an inability to face stress normally (allostasis), this exhaustion of the HPA axis has important clinical consequences, for example, being at risk for heart problems, high blood pressure, infections, work accidents, and—very likely—auditory dysfunctions, such as tinnitus.

Fazit

Klinische Studien zeigen, dass Tinnitus mit erheblicher Fehlsteuerung der HPA-Achse assoziiert ist, ähnlich wie es bei anderen stressbedingten Erkrankungen festgestellt worden ist. Möglicherweise werden die Basalwerte des Cortisolspiegels zunächst erhöht und chronische Stressexposition kann durch eine erhöhte Empfindlichkeit gegenüber negativer Rückkopplung zu einer verringerten akuten Stressantwort und HPA-Achse-Dysregulation führen. Neben der Unfähigkeit, physiologische Antworten auf Stress zu entwickeln (Allostase), hat die Dysregulation der HPA-Achse wichtige klinische Folgen, wie die Erhöhung eines Risikos für Herz- und Kreislauferkrankungen, Infektionen und Bluthochdruck, häufigere Arbeitsunfälle und auch auditorische Effekte, wie Tinnitus.

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Compliance with ethical guidelines

Conflict of interest. B. Mazurek, A.J. Szczepek, and S. Hebert state that there are no conflicts of interest. All national guidelines on the care and use of laboratory animals have been followed and the necessary approval was obtained from the relevant authorities.

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