The effects of acute and chronic stress on auditory function: Experimental and clinical studies

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The deleterious effects of mechanical stress (i.e. noise) on hearing have been studied extensively in both animal models (Ohlemiller, 2008) and human populations (Tambs *et al*., 2003) but the notion of emotional stress as a modulator of the auditory system is rather novel. A complex set of pathways of the stress response have been identified, involving both sympathetic stimulation of adrenergic α-receptors within the cochlea (Bielefeld and Henderson, 2006), as well as neuro-endocrine responses primarily aimed at engaging the hypothalamic-pituitary-adrenal (HPA) axis. Current research suggests that acute stress may protect the cochlea (Tahera *et al*., 2006, 2007), whereas chronic stress exposure seems to be harmful to hearing. The importance of a normal functioning of the stress response for healthy hearing is supported by clinical studies showing that patients with tinnitus display signs of an impaired stress response along with a higher degree of perceived stress, compared to non-tinnitus patients (Hebert and Lupien 2007, 2009). In this review we discuss how acute or chronic stress can modulate the auditory system. Our results cover a range of experimental studies as well as several clinical studies and will be presented separately.

EXPERIMENTAL STUDIES

The hypothalamic-pituitary-adrenal axis (HPA) mediates responses to different stressors. The HPA involves a negative feedback system that includes the para-ventricular nucleus of the hypothalamus which responds to stressful signals from the limbic system, brain stem and other brain regions by activating different hormones including corticotrophin-releasing hormone (CRH) and arginin vasopressin (AVP). These peptides trigger the release of adrenocorticotrophin hormone (ACTH) from anterior pituitary which, in turn, activates the synthesis and secretion of glucocorticoids (GCs) from the adrenal glands (Fig. 1). Cortisol is the predominant GCs in humans whereas corticosterone (CORT) dominates in rodents. The concentration of CORT in the blood has a specific pattern depending of the species and diurnal activity. Once CORT enters the cytoplasm the enzyme, 11β-hydroxylase, controls the availability of CORT to not activate the high affinity mineralcorticoid receptor thereby allowing access for the glucocorticoid receptor (GR) (Seckl and Meaney, 2004). GRs are ubiquitously expressed in almost all human tissues and organs. They are found in the cochlea and localized primarily to the hair cells, spiral ganglion neurons and the spiral ligament (Meltser *et al*., 2009).

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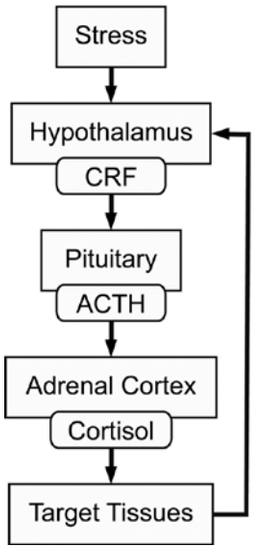

Fig. 1: The synthesis and secretion of the glucocorticoids (CORT: cortisol in humans, corticosterone in rodents) is tightly controlled by negative feedback mechanisms. The negative feedback mechanism is an effective feature of hormone secretion that is regulated by the hypothalamus and the pituitary gland. When hormone is released it will bind to receptors in the hypothalamus and cause an inhibition of corticotrophin-releasing (CRH) hormone and adrenocorticotropic (ACTH). The negative feedback system results in hormonal homeostasis by reducing CRH secretion that in turn, results in a reduction of ACTH release that will inhibit CORT secretion from zona fasciculate of the adrenal gland into the blood stream.

The synthesis and secretion of the GCs is tightly controlled by negative feedback mechanisms. This negative feedback system is an important feature of hormonal homeostasis and occurs by reducing CRH secretion and ACTH release. As a result the reduction in CRH and ACTH release will then inhibit CORT secretion from the adrenal glands (Herman and Cullinan, 1997). Glucocorticoids enter the cell and bind to glucocorticoid receptors (GR) which results in the activation of the receptor which then translocates into the nucleus. Once in the nucleus, GR binds to the glucocorticoid response elements (GRE) that results in the modulation of transcription factors. There are several different ways in which the activity of GR can be inhibited. Pharmacological inhibition occurs by using the glucocorticoid synthesis inhibitor, metyrapone and the GR antagonist, RU 486.

Effects of acoustic trauma and glucocorticoid responses

Acoustic trauma results in a rise in CORT levels in the blood in rodents (Tahera *et al*., 2006a). As a result of the rise in CORT the tissues expressing GRs will be activated. In order to determine if GRs in the cochlea are affecting auditory sensitivity we treated mice with either with a glucocorticoid antagonist (metyrapone + RU 486) or a glucocorticoid agonist (DEX) prior to an acoustic trauma (6–12 kHz) for 45 min at intensity of 100 dB (dB SPL) (Tahera *et al*., 2006a). The immediate-after effects of acoustic trauma on ABR thresholds showed statistically significant differences between the vehicle + acoustic trauma group and the drug (metyrapone + RU 486) + acoustic trauma group at 8 kHz, 12 kHz, and 16 kHz ($P < 0.001$). The vehicle group (filled circles) demonstrated threshold shifts between

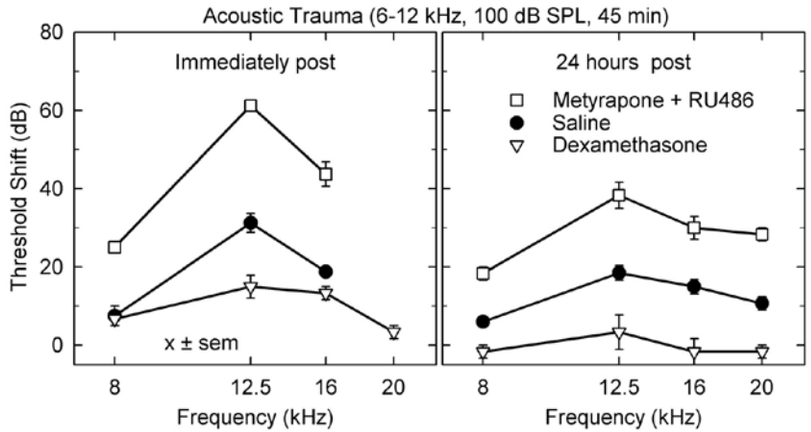

Fig. 2: Mean ABR threshold shifts were obtained by comparing pre-exposure thresholds with post-exposure thresholds. Left: Immediate post-trauma ABR threshold shifts. Pre-exposure treatment with metyrapone + RU 486 (open squares) resulted in the greatest threshold shifts compared with vehicle (saline) treated group (filled circles), or the dexamethasone group (open triangles). Right: 24 hr post trauma the ABR threshold shift was significantly more elevated in the group pre-treated with metyrapone + RU 486 compared with vehicle group. The dexamethasone treated group showed near complete recovery.

10–30 dB across frequencies, whereas the threshold shifts from the drug-treated group (open squares) were between 25–60 dB (Fig. 2). Animals pre-treated with dexamethasone, a synthetic glucocorticoid, were protected against acoustic trauma and showed a 7–12 dB change from pre-exposure thresholds (open triangles). The mean threshold value at 12.5 kHz from the dexamethasone group was statistically significant from the vehicle group (Tukey test $P < 0.003$). The dexamethasone treated animals showed statistically significant thresholds from the drug-treated group at all frequencies (Tukey test $P < 0.001$).

After a 24 h recovery period the thresholds from all groups showed partial to complete recovery. The DEX-treated group showed complete recovery, whereas the vehicle group continued to show a 6–18 dB shift, and the drug-treated group (metyrapone + RU 486) continued to show between 18 and 38 dB threshold shifts (Tahera *et al*., 2006a).

There are several different possible mechanisms for these physiological effects but one likely explanation includes an inhibition of the anti-inflammatory effect of corticosteroids. Several studies have shown the presence of inflammatory cells and proinflammatory cytokines in the cochlea after acoustic trauma (Fredelius and Rask-Andersen, 1990) and also in patients with autoimmune sensorineural hearing loss (Gloddek *et al*., 2002). It is well known that corticosteroids are inhibitors of inflammatory cytokines synthesis and release and antagonize the intracellular effects of cytokines (Maeda *et al*., 2005).

Prenatal treatment with glucocorticoids causes permanent alterations in auditory sensitivity

Studies from both humans and animals demonstrate that adverse fetal development can permanently cause disturbances in the programming of the HPA axis in adult life (Barker, 1998; Godfrey, 1998; and Welberg and Seckl, 2001). Prenatal exposure to glucocorticoids can affect fetal growth and metabolism that can permanently alter stress responses in adult life. Examples of these effects include increased risks for hypertension, glucose resistance leading to heart disease, diabetes, and emotional and neuroendocrine disturbances in adult life. Similar effects are found for experimental animals (Seckl, 1998).

We have previously shown that prenatal treatment with glucocorticoids affects the auditory system in animals (Hossain *et al*., 2008). The paradigm was such that animals were treated from day 14 of pregnancy until parturition with either saline or 0.1 mg/kg body weight dexamethasone (Canlon *et al*., 2003). This treatment modifies the HPA axis of the offspring and leads to lifelong alterations in mammalian species. The effect of prenatal treatment results in an altered expression of glucocorticoid receptors throughout the body causing lower levels of cortisol (in humans) and corticosterone (rodents). This prenatal treatment reduces body weight at birth in a sex-dependent manner. In addition, the adrenal glands from the male treated group were smaller than the control males and the control females as well as the treated females (Hossain *et al*., 2008).

It has been demonstrated that the auditory system shows increased susceptibility to acoustic trauma in animals prenatally treated with dexamethasone (Canlon *et al*., 2003). When the animals were exposed to an acoustic trauma the ABR thresholds, when measured immediately after exposure, were similar for both groups. Both the control (saline) and the treated (dexamethasone) animals showed elevated thresholds at all frequencies of equal magnitude (DEX: 30–48 dB; SAL: 27–49 dB) (Fig. 3). However, when thresholds were determined either 48 h or 4 weeks post-exposure the saline treated rats showed significant improvements in auditory thresholds while the DEX rats showed little recovery. At one month post-trauma

the dexamethasone animals continued to show significantly greater permanent threshold shifts at all frequencies (DEX: 21–36 dB) while the control group returned to pre-exposure thresholds.

These studies demonstrated that manipulations to the intrauterine environment can modify the developmental programming of the cochlea by causing dysfunction later in adult life. Prenatal exposure to dexamethasone decreased the ability to recover from the acoustic trauma which could be counteracted by treatment with antioxidants Canlon *et al*., 2003).

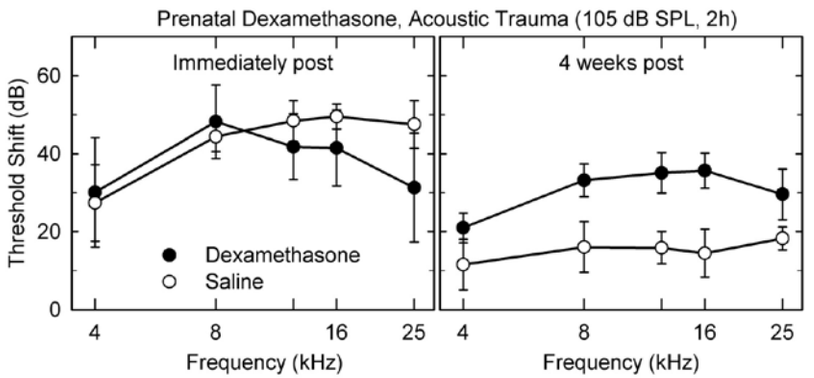

Fig. 3: The auditory system has increased susceptibility to acoustic trauma in animals that are treated prenatally with the glucocorticoid receptor agonist, dexamethasone. When the offspring were 2 months old they were exposed to a moderate acoustic trauma. When ABR thresholds were measured immediately after exposure both groups (saline and dexamethasone) showed elevated thresholds overall frequencies of equal magnitude (DEX: 30–48 dB; SAL: 27–49 dB). However, when thresholds were determined 4 weeks post-exposure the Saline treated rats showed significant improvements in auditory thresholds while the DEX rats showed little recovery.

CLINICAL STUDIES

The individuals included in this study were obtained from the Swedish Longitudinal Occupational Survey of Health (SLOSH) (Magnusson *et al*., 2008), which was initiated by the Stress Research Institute in 2006. The second data collection was conducted in April 2008 by Statistics Sweden, on behalf of the Stress Research Institute at Stockholm University. A total of 18,734 individuals were mailed self-completion questionnaires in 2008, out of which 9,756 (52%) working individuals responded. The total response rate of the study was however 11,441 (61%), including non-working participants (not analyzed in the present study).

Questionnaire

The participants answered a questionnaire including socioeconomic status, demographic factors, and questions about psychosocial and physical work-environment, lifestyle, as well as physical and mental health. Hearing problems were assessed with three questions. *Tinnitus*. Have you during the most recent time experienced sound in any of the ears, without there being an external source (so-called tinnitus) lasting more than five minutes? (No, Yes sometimes, Yes often, Yes all the time). *Tinnitus severity*. How much do you feel that the tinnitus sounds worry, bother or upset you? (Not at all, A little, Moderately, Severely). The questions about tinnitus were adapted from Davis (1989) and Palmer *et al*. (2002). *Hearing complaints*. How difficult is it for you to (without hearing aid) hear what is said in a conversation between several persons? (Not difficult at all, Not very difficult, Quite difficult, Very difficult). In this study, hearing complaints reflects difficulties in communicating. A new variable, "hearing problems", was computed based on the existence or non-existence of either tinnitus or hearing complaints or both. This consequently yielded three groups; those without hearing problems, those with either tinnitus or hearing complaints or those suffering from both. The cut-off for tinnitus was "yes, sometimes" or more often, and for hearing complaints "quite difficult" or "very difficult". The questions related to work and stress included risks of being moved to another work/job against ones will, threats of getting fired or threats of bankruptcy. The question was formulated: "Are you subjected to any of the following risks or threats in your work?" Response alternatives were yes/no.

Burnout was assessed with the Maslach Burnout Inventory general survey (MBI-GS) using the emotional exhaustion subscale (Maslach, 1996). The scale consists of five items, derived from the Maslach Burnout Inventory human services survey (MBI-HSS) in unmodified form. Scorings reach from 1 (every day) to 6 (a few times a year or less/never). The index was calculated on the basis that 4 out of 5 items had to be answered in order be included in the index.

Long lasting stress (LLS) was assessed with 11 items reflecting stress arousal symptoms but not stress reactions. The participants were asked how they felt during the last three months with regard to both physiological (e.g. "I sweat easily even though I do not exert myself physically") and cognitive-behavioral symptoms (e.g. "I have worrying thoughts"; "I often feel tense"). The four response alternatives reached from "Not at all" to "Nearly all the time". The scale was introduced in the 2008 SLOSH questionnaire and is currently being validated. A factor analysis yielded one factor of interest. This factor included 7 of the 11 items and only the cognitive-behavioral symptoms. Factor loadings ranged from .675 ± 798 and a Chronbach's α of .863. The 7 included items were (including factor loading, FL): A) I have days when I feel geared up all the time (FL = .675). B) I have days when I feel very pressured, on the verge of what I can handle (FL = .737). C) I find it hard to relax during my leisure time (FL = .787). D) I often feel tense (FL = .798). E) I often have disturbing thoughts (FL = .768). F) I often feel restless (FL = .720). G) I do not feel rested after taking it easy for a few days (FL = .699).

RESULTS

Overall, the results describe an association between hearing problems and work- and health-related stressors (Hasson *et al*., 2011). All the results were controlled for possible confounding effect of age, gender or SES with multivariate analyses. These analyses showed no confounding effect of these variables. The demographics of the population in the present study are as follows: 4,462 (46%) men and 5,294 (54%) women. The mean age was 48.6 (± 10.8) for men and 48.2 (± 10.5) for women. Age distribution was: under 40 years 1,148 (26%) men and 1,314 (25%) women; 41 ± 51 years 1,202 (27%) men and 1,520 (29%) women; 51-60 years 1,415 (32%) men and 1,754 (33%) women; 60 years or older 697 (26%) men and 706 (13%) women. Marital status: married 2,491 (56%) men and 2,946 (56%) women; unmarried 1,494 (34%) men and 1,516 (29%) women; divorced 444 (10%) men and 726 (14%) women; widow 33 (1%) and 106 (2%) women. With regard to highest completed educational level, 1,016 (10%) had no gymnasium, 4,510 (46%) had gymnasium, 619 (6%) had undergraduate studies of two years or less, 3,472 (36%) had undergraduate studies of three years or more and 134 (1%) hade post graduate studies.

Burnout

The prevalence of hearing problems between those with higher burnout scores compared to those with lower scores was statistically different ($\chi^2 = 214.473_{df = 6}$, $p < 0.0001$, for women $\chi^2 = 159.205_{df = 6}$, $p < 0.0001$, for men: $\chi^2 = 98.935_{df = 6}$, $p < 0.0001$). Hearing problems were significantly more prevalent among those with higher burnout scores. Multivariate analyses showed no age, gender or SES related differences in prevalence increases with increasing burnout scores.

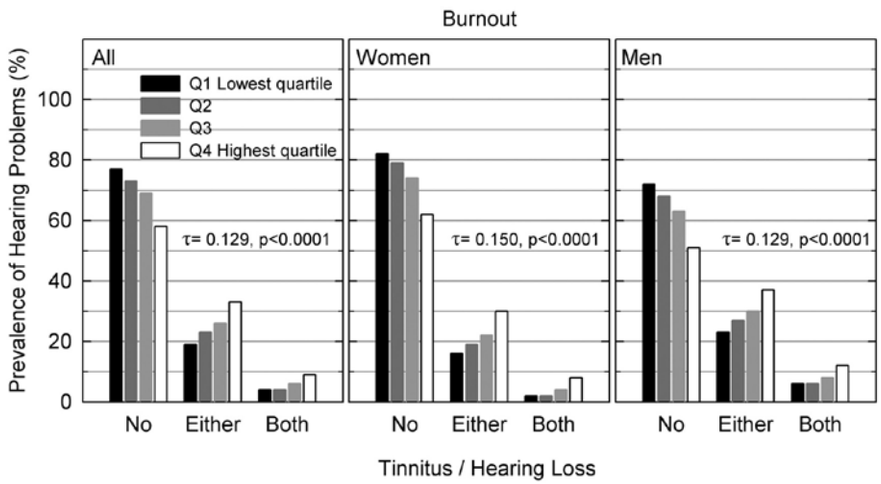

Fig. 4: Prevalence of hearing problems in percent in relation to different burnout scores (higher quartiles indicate more severe burnout symptoms).

The association was positive (for all: Kendall's τ-b = 0.129 $p < 0.0001$, for women: Kendall's τ-b = 0.150 $p < 0.0001$, for men: Kendall's τ-b = 0.129 $p < 0.0001$) and figure 4 demonstrates that higher burnout scores are associated with a higher prevalence of hearing problems. The proportional odds model did not exhibit any differences in odds ratios when age and socioeconomic status were included in models for neither women nor men. For example, the unadjusted odds ratio of having hearing problems when being in the highest vs. lowest burnout quartile were 2.36 for men ($p < 0.001$) compared to the adjusted odds ratios which were 2.63 ($p < 0.001$). For women, the corresponding values were 2.80 ($p < 0.001$) and when adjusted the value was 2.79 ($p < 0.001$).

A statistically significant difference in the prevalence of hearing problems between those with more symptoms of long-lasting stress scores compared to those with less was found ($\chi^2 = 196.855_{df = 6}$, $p < 0.0001$, for women $\chi^2 = 145.608_{df = 6}$, $p < 0.0001$, for men: $\chi^2 = 90.613_{df = 6}$, $p < 0.0001$). Hearing problems were more prevalent among those with more symptoms of long-lasting stress. Similarly to the pattern for burnout, the prevalence increase was higher for women than for men, even if it was less pronounced for this variable. The association was positive (for all: Kendall's τ-b = 0.127 $p < 0.0001$, for women: Kendall's τ-b = 0.148 $p < 0.0001$, for men: Kendall's τ-b = 0.126 $p < 0.0001$) and figure 4 demonstrates that more symptoms of long-lasting stress are associated with a higher prevalence of hearing problems.

Burnout and symptoms of long-lasting stress

This study has demonstrated a relation between stress-related disorders, such as burnout and hearing problems. Moreover, the results showed clear associations between burnout as well as symptoms of long-lasting stress and hearing problems. Furthermore, hearing problems were also more common among those with long-term illness, pains, inconveniences or handicaps. This strengthens the hypothesis about high levels of co-morbidity among individuals with hearing problems. The relation between long-term stress and tinnitus has been previously explored and tinnitus sufferers often report enhanced problems by stress and fatigue. However, it is not yet known if tinnitus is a direct or indirect response of the auditory system to stress. A major therapeutic strategy for tinnitus patients includes relaxation programs which have proven successful for many sufferers. Thus, taking into consideration the results of individuals with hearing problems (hearing complaints and tinnitus) of the present study and findings from prior tinnitus studies, it is becoming more apparent that stress can increase the prevalence of hearing problems. It has also been shown that individuals with hearing problems have a worsened ability to unwind and activate the parasympathetic system.

Finally, this study demonstrates associations between hearing problems and occupational stressors, poorer self-rated health, higher burnout scores, and more symptoms of long-lasting stress. The interaction between the prevalence of hearing problems and the above mentioned features have not been previously described for the auditory system. These findings also indicate that hearing problems are multidimensional, which warrants further investigations of possible predictors.

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