Transient decrease in sound tolerance levels following hearing deprivation in normal-hearing subjects

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1. Introduction

Hyperacusis is defined as an abnormally reduced tolerance to common environmental sounds or an uncomfortable increment of loudness perception at sound levels that are comfortably perceived by others (Baguley, 2003; Chen et al., 2013; Niu et al., 2012). While the exact pathophysiology is unknown, one of the prevailing theories that could explain the origin of hyperacusis is known as the Central Gain Model, which will be explored in this study. The Central Gain Model proposes that hyperacusis results from a mal-adaptation of the central auditory system after cochlear damage occurs. The central auditory system, consisting of the inferior colliculus, medial geniculate body, and auditory cortex, has been observed to have increased neural activity in response to the decreased sensory output from the damaged peripheral auditory system (Auerbach et al., 2014; Radziwon et al., 2019).

Reports of the prevalence of hyperacusis are found to be inconsistent among authors; some questionnaire-based studies have reported a prevalence ranging from 0.2% to 17.2% in the adult population (Andersson et al., 2005; Baguley, 2003; Joris, 2009; Ren et al., 2021; Rubinstein et al., 1996). Several medical conditions such as Bell’s palsy, head injury, Lyme disease, and Williams syndrome...
can be associated with hyperacusis (Paulin et al., 2016; Tyler et al., 2014). Furthermore, hyperacusis is considered a disorder of plasticity that is closely associated with tinnitus (Khalfa et al., 2004; Oen et al., 1997; Rosenhall et al., 1999). Approximately 40% of patients with tinnitus also complain of hyperacusis, regardless of age group. Meanwhile, 86% of patients complaining of hyperacusis have or will develop tinnitus (Baguley, 2003).

Several mechanisms have been postulated as being involved in the increase of auditory central gain, leading to the development of hyperacusis and tinnitus. A few studies have suggested that after deprivation of auditory inputs following experimentally induced hearing loss with earplug use or acquired clinical hearing loss, the postsynaptic membrane becomes hyperexcitable, increasing its spontaneous firing rate. These findings are supported by the fact that hearing loss of as little as 20 dB can lead to an increase in neural activity in the auditory system (Gerken 1996). In contrast, a benzodiazepine model unrelated to auditory input deprivation mimics the compensatory homeostatic plasticity mechanism, leading to increased auditory central gain. Long-term use of benzodiazepines results in an increase in the affinity of γ-aminobutyric acid (GABA) for its receptors (GABA-R), causing predominantly inhibitory neurotransmission (auditory input deprivation). This could result in hyperacusis and tinnitus when the medication is abruptly stopped.

The circadian rhythm may affect the CNS auditory pathways because the activity of outer hair cells is modified during the day (Al-Mana et al., 2008; Urnau and Tochetter, 2012). A study by Park et al. (2016) demonstrated that neurons in the inferior colliculus express different levels of mRNA and proteins depending on day or night sound exposure, showing that the inferior colliculus expresses some circadian clock-related genes. The cochlea has also been found to express a circadian clock and regulates differential sensitivity to noise in the day versus in the night. Another CNS area involved in regulating wakefulness and thought to interact with the auditory system and its related capacity to hearing in noise and selective attention is the ascending reticular system. This formation is also involved in the stress response and expresses adrenal steroid receptors. Therefore, glucocorticoids may also influence auditory function by interacting with receptors found in the brainstem nuclei, including the mesencephalic raphe and locus coeruleus, which contain serotoninergic and noradrenergic neurons (Al-Mana et al., 2008). Serotonin is thought to be the main neurotransmitter involved not only in central gain but in the determination of the significance of sound (Baguley, 2003; Baguley et al., 2013; Noreña, 2011). Another study found that women with higher levels of emotional exhaustion reported higher uncomfortable loudness levels (ULL) and hyperacusis after acute stress exposure (Hasson et al., 2013). Conditions such as tiredness, anxiety, or stress may generate endogenous dynorphins that are released into the synaptic region beneath inner hair cells, which might potentiate the neurotransmitter glutamate (Kuba et al., 2010; Noreña, 2011).

No previous study has directly or indirectly described the effect of compensatory central gain if hearing deprivation is produced during daytime or nighttime, considering the difference of cortical and subcortical activity in those conditions. The aim of this study is to determine the circadian influence on sound sensitivity produced by temporal hearing deprivation in healthy normal human subjects.

2. Materials and methods

2.1. Ethical considerations

After protocol approval by the Bioethics Committee of the Venezuelan Foundation of Otorlgy (FVO), informed consent was obtained from all subjects.

2.2. Population and design

Thirty volunteers between 15 and 30 years old were enrolled in this study. Four subjects were excluded because they met at least one exclusion criteria. This prospective study included baseline and follow-up testing of serum cortisol levels, psychoacoustic, and psychophysical hearing measures. Psychiatric and emotional assessments were also performed. Subjects were randomly divided into two groups. Bilateral occlusion was made by placing a Foam Ear Plug NRR (Noise reduction ratio) – 30 dB C-weighted OSHA in the ear canal, which was covered with bacitracin ointment. Cotton wool and an Opticlude® (3M, Minnesota, USA) eye dressing was placed to cover all the conchae and helix areas for a total assessed attenuation of 28.3 dB SPL. The first group (group A) started at 8:00 a.m. and finished at 8:00 p.m., and the second group (group B) started at 4:00 p.m. and finished at 4:00 a.m. Blood samples were taken to have two points of reference during occlusion, including the lowest and highest levels of cortisol in a 12-h time frame, as regulated by the circadian cycle. A 24-h urine sample, from 8 a.m. to 8 a.m. the following day will indirectly measure if the total cortisol in the cycle was appropriate and not interfered by other factors such stress. During the development of the protocol, the subjects were hospitalized at the FVO in-patient facility in a quiet and controlled environment, and regular balanced meals were taken. The acoustical environmental condition was as follows: from 8 a.m. to 8 p.m., average metered conditions of 63 dB SPL and a peak of 86 dB SPL; and from 4 p.m. to 4 a.m., average metered conditions of 54 dB SPL and a peak of 78 dB SPL. Immediately after the 12-h period was completed, the subjects were taken to a soundproof booth where the foam ear plug was removed, and all psychoacoustic tests were repeated.

2.3. Data collection

Prior to the hearing and blood tests, the subjects completed a questionnaire created by the authors, which was administered by a clinician and included 16 questions, 13 of which had a dichotomy design, and three related to the number of hours dedicated to physical and work-study activities. Anthropometric measures such as height, weight, and body mass index (BMI) were obtained to exclude subjects over 25 kg/m² of BMI to rule out any glucocorticoid metabolic-related problem (see Table 1). Questions 14 to 16 ruled out the presence of tinnitus and/or hyperacusis as part of the exclusion criteria.

2.4. Psychiatric assessment

Likewise, the Hamilton Anxiety Scale and Depression Inventory were given to all subjects; the cut-off value was ≥12 points and ≥7 points, respectively, to rule out depression and anxiety, symptoms strongly associated with hyperacusis.

2.5. Hearing assessment

2.5.1. Psychoacoustic tests

Bilateral hearing status was assessed before and immediately after hearing deprivation using a pure tone audiogram (PTA) following the standard Hughson–Westlake procedure; 125, 250, 500, 1,000, 2,000, 4,000, and 8,000 Hz frequencies were tested for air conduction, and 250, 500, 1,000, 2,000, and 4,000 Hz frequencies for bone conduction using a CSI-61 audiometer® (Grayson–Stadler, Minnesota, USA) and TDH-39 headphones. Speech audiometry was also assessed with speech recognition and
discrimination thresholds using phonetically balanced trisyllabic and monosyllabic words in an open set environment. Bilateral uncomfortable loudness level (ULL) thresholds were done where each participant was instructed to let the examiner know when the narrow band noise (NBN) became uncomfortably loud by speaking into a microphone. The testing started with the NBN at 1.000 Hz, with an intensity of 70 dB SPL. When a particular sound intensity was perceived as uncomfortably loud, decrements of 10 dB SPL were followed for the testing of the succeeding frequency. As the db SPL decreased, the process was reversed for the frequencies tested later on, in which the sound intensity was increased in 5 dB SPL steps until the subject reported the sound as uncomfortably loud. 

The tested frequencies were 500, 1000, 2000, and 4,000 Hz (Hasson et al., 2013).

### 2.5.2. Non-psychoacoustical tests

To assess the status of middle ear function, tympanometry and stapedial reflex thresholds (SRT) (500–4,000 Hz, ipsi and contra-lateral) were evaluated using a Danplex TYPMP87k® impendanciometer (Precision Acoustics, Cloverdale, Australia). Distortion products of otoacoustic emissions (DPOAE) were measured using a GSI Audera system®. Input/output function was tested at 2,378.4 Hz ($f_2 = 2,000$ Hz) where the most robust responses were found in normal hearing subjects as well as less noise floor, based on the frequency specific standard $[(L_1(f_2)L_2)^a(f_2)L_2 + b(f_2))]$, starting from 20 dB SPL and increasing to 65 dB SPL, with a 5 dB SPL increase interval.

### 2.6. Samples for cortisol analysis

Patients were instructed not to drink alcoholic beverages and to avoid medications for at least 48–h prior to blood extraction. Venous blood samples were collected pre-and post-occlusion. Samples were centrifuged at 2,500 revolutions per minute (r.p.m.) for 10 min; plasma was collected and subsequently preserved at −80 °C. For determination of cortisol hormone content, a solid phase competitive chemiluminescent enzymatic immunoassay was performed with IMMULITE 2000® (Siemens Healthcare Diagnostic Products, Llanberis, United Kingdom). Reference values were 28-71 μg/mL from 8 a.m. to 8 p.m. (group A) and 18-2 μg/mL from 4 p.m. to 4 a.m. (group B).

Twenty-four-hour free urinary cortisol level was also measured with 12 mL aliquot from the total urinary volume of each participant. The aliquots were centrifuged at 2,500 r.p.m. for 10 min, and 10 mL of the supernatant stored at −80 °C. For determination of cortisol levels, IMMULITE 2000® (Siemens Healthcare Diagnostic Products, Llanberis, United Kingdom) assay was performed. The normative value was 9–100 μg/24 h. The reason for these measures is that cortisol before reflects the endocrine cycle status, the glucocorticoid response to stress, and the wide distribution of the glucocorticoid receptor (GR) in the CNS, especially auditory-related.

### 2.7. Statistical analysis

A t-test was performed between groups (A and B) to rule out differences regarding biometrical, daily activity, exercise, sleep, and work variables ($p<0.05$), and two-way analysis of variance (ANOVA) test followed by a post-hoc Tukey multiple comparison test were used for comparative analysis of the measured psychoacoustic parameters between the groups ($p<0.01$). For the analysis of parametric variables, a non-linear regression analysis was performed to analyze cortisol levels. GraphPad Prism 5.0c® (GraphPad Software, Inc., California, USA) was used for all statistical calculations and graph construction.

### 3. Results

A total of 26 subjects out of 30 who enrolled (17 females and 9 males) met the inclusion criteria. Both groups were homogeneous in all the biometric variables (i.e. age, weight, height, and BMI) ($p > 0.05$). Daily activities, sleep, work, and exercise between both groups were also not significantly different ($p > 0.05$). No depression or anxiety was found in either group.

#### 3.1. Hearing threshold decreases after hearing deprivation

PTAs reflect lower thresholds in post-occlusion conditions. Such a difference was observed in both groups, with a range of 1.25–2.68 dB HL for group A and 1.45–3.33 dB HL for group B. This shift was statistically significantly different at 125 Hz–500 Hz in group A ($p = 0.0007$) and 250 Hz to 1,000 Hz in group B ($p = 0.0009$). However, there was no statistically significant difference between day (group A) and night (group B) ($p = 0.4947$) (Fig. 1A and B).

#### 3.2. Hearing deprivation during the day is associated with hypersensitivity to sound

ULLs showed a significant threshold shift at all frequencies, with a mean value of 100.7 dB SPL (standard deviation [SD] 0.2965) pre-occlusion and 92.81 dB SPL (SD 1.329) post-occlusion ($p < 0.001$) for group A (Fig. 2A). Group B only demonstrated a significant supra-threshold shift at 4,000 Hz of −3.12 dB SPL (SD 1.040; $p < 0.001$) (Fig. 2B). Inter-group and inter-frequency comparisons were extremely significant ($p < 0.0001$) (Fig. 2C).

#### 3.3. SRT shows influence with daytime hearing deprivation

Contralateral recordings of the stapedial reflex threshold (SRT) were found in 90.13% of the patients. A significant difference was observed in group A at 2,000 Hz (−3.21 dB SPL, SE 0.91) and 4,000 Hz (−3.22 dB SPL, SE 0.91) ($p < 0.001$) (Fig. 3A). Group B showed no difference between pre- and post-occlusion ($p = 0.5854$) (Fig. 3B). The difference between group A and group B was not statistically significant ($p = 0.1413$).

#### 3.4. DPOAEs are not affected by hearing deprivation

DPOAEs were not significantly affected in any of the conditions. However, a lower response after occlusion was found at 2,378 Hz
input/output function in group B (Fig. 4A and B). A weaker response was seen in this group, with a difference of −0.85 dB SPL at almost all intensities. Even though the difference was not statistically significant (p = 0.0248), the trend of a lower amplitude of DPOAE was systematically present in 85% of the subjects at night (group B).

3.5. Cortisol levels suggest a normal circadian pattern

Cortisol levels were within normal limits. Urinary cortisol showed an insignificant difference of 9.2 μg/dL total. Group A showed a decrease in cortisol levels from its peak to its nadir. Group B’s cortisol levels rose from its lowest value to its peak (Fig. 5A). Once correlated, the results are highly dependent on each group (r = 0.7216; p < 0.0001) (Table 2).

4. Discussion

Hyperacusis is a common condition associated with abnormal activity within the central auditory system resulting in the sensitivity to ordinary sounds (Baguley et al., 2013). It is often reported by patients whose hearing thresholds improve after exposure to some degree of hearing deprivation, such as in stapes surgery, in hearing-aid users with a prolonged period of non-use, and in patients with earwax occlusion after its removal (Formby et al., 2003; Hamilton and Munro, 2010; Munro and Blount, 2009).

Several auditory molecular mechanisms are associated with the sensation of hearing deprivation following the act of ear occlusion (Samhie and Nodar, 2001). The CNS can respond in two possible ways to sound deprivation: it can respond with an increase in response gain (synaptic strength), maintaining the stable neuronal circuit, or it can respond with a failure to appropriately adapt the central response gain, which may cause the perception of hyperacusis (Knipper et al., 2013). The effects of hearing attenuation on threshold shift after ear occlusion measured by PTA are not well understood. Some recent studies state that patients with hyperacusis had a generalized increase in sensitivity or response to sound across the hearing range (Alain et al., 2015; Sheldrake et al., 2015). Despite the lack of data, lower frequencies are the most affected and in our research are statistically, though not clinically, significant in the range of 125 Hz to 1,000 Hz, with an average shift of −2.78 dB HL. Our study team recognizes the limitation regarding the lack of control groups in this investigation. Most studies of a pre and post exposure to a very-well known factor do not warrant a control. Control groups are important when randomizing and blinding from the test variable, which was not possible in this study design. Incorporating both AM and PM control groups posed...
several technical difficulties and logistical challenges. As such, the measurements taken for each subject, pre-plugging, served as a baseline in this investigation.

Hypersensitivity at the threshold level could have two possible explanations: If we consider that its function is related to otoprotection from overstimulation, the lack of stimulation may result in reduced activity within the medial efferent system and thus demonstrate auditory effect pathway involvement. (Guinan, 2006; Noreña, 2011). On the other hand, biochemical changes within the peripheral auditory system could play an important role in this temporary hypersensitivity in the same way that hyperacusis is produced as an augmentation of glutamate by the inner hair cells that boost its excitatory activity, leading to an increase of intensity perception (Baguley, 2003).

Interestingly, DPOAE results did not demonstrate a significant difference in the present study, as only a slight difference was seen at night at 2,378 Hz input/output function, with a minimal and marginal difference in the slope. The changes in ULL seen in this study after hearing deprivation have been described in hyperacusis patients, with a shift to lower threshold ranges between 16- and 18-dB SPL in previous studies compared with normal, non-hyperacusis subjects. In this case, we agree with previously published findings stating that hypersensitivity to sound is more likely to be regulated by central gain without excluding peripheral inner and outer hair cell function (Al-Mana et al., 2008; Kumagami et al., 2013).

An interesting result within this study shows a significant decrease of the ULL threshold during the day in all frequencies after hearing deprivation, in contrast with the hearing-deprived group during the night (group B). It has been hypothesized that the auditory cortex is highly active during the day due to awareness conditions. Animal models have demonstrated sensory stimuli do
not trigger behavioral responses and are not consciously perceived during wakefulness conditions (Alain et al., 2015; Nir et al., 2015). If hearing deprivation occurs during that time, the auditory cortex tends to be more sensitive to sound to compensate for the peripheral loss; this is essentially the central gain mechanism detected in our subjects after daytime hearing deprivation (group A). However, no significant difference in ULL was seen in the night group (group B). During this period of time, our subjects experienced less sensitivity to sound after deprivation at the suprathreshold level, which can be explained by the fact that the auditory cortex is less active during nighttime sleeping and could be translated into less central gain. One mechanism that could explain this is the sleep disconnection due to a thalamic ‘gate’ which would prevent signal propagation along ascending sensory pathways to primary cortical areas (Nir et al., 2015). It is worth mentioning that every condition that could initiate any stressful situation was ruled out in our subjects prior to hearing occlusion, neither acute nor chronic; and even in the absence of the latter, a meaningful decrease in the ULLs was detected, a new finding in a completely different setting as those described by the patients with emotional exhaustion, and the related changes in cortisol secretion in response to stressors (Hasson et al., 2013). However, anxiety secondary to hearing occlusion cannot be ruled out. This difference is less evident in the stapedial reflex response, in which our series did not show any significant difference between groups, which could indirectly suggest that this hypersensitivity is centrally mediated and the brainstem, where the stapedial reflex is based, is not affected by sleep or cortical activity; this confirms that in some individuals middle ear reflexes are not affected by hyperacusis (Alain et al., 2015; Sheldrake et al., 2015). According to recent studies, hearing input fixation is important, as auditory learning involves a consolidation phase that occurs during the awake state, which is followed by a sleep-dependent consolidation stage (Alain et al., 2015). Inversely, as the sleep pattern becomes superficial, much higher cortical activity and rising levels of cortisol increase our awareness. Patients with long-term obstructive earwax have reported hyperacusis after its removal. Similar findings were observed in other studies with a longer period of hearing attenuation (Noreña, 2011). Our findings demonstrate that the pattern of sensitivity to sound changes with nighttime deprivation (group A versus B); this has not been reported previously, possibly because most of the patients in a longer period of attenuation were tested during the day. Another factor that affects experimental models in humans is the possible increase in anxiety with long periods of earplugging and some adaptation and learning process in longer periods of time.

Our data also suggests that central gain can be regulated by adaptation and might be downregulated by subcortical activity. In normal-hearing subjects, this adaptive process is not usually detected but could be revealed by induced hearing deprivation. This can be extrapolated into the clinical setting as transitory hyperacusis felt by patients after stapes surgery as well as with a hearing device fitting, such as a hearing aid or cochlear implant. Individuals who use hearing devices are advised to turn their units off before bedtime, in turn, these patients experience a form of temporary hearing deprivation on a daily basis. However, based on the premise that central gain is reduced during nighttime or sleep, some patients reported that they need some time for adaptation when they turn their device on in the morning. This transient hyperacusis could be prevented by baseline auditory or electrical stimulation.

In our study, cortisol levels in the bloodstream and urine reflect only indirectly a normal circadian pattern in the subjects. Any findings related to a direct effect of cortisol and hearing cannot be determined by any of the findings in this study, but the presence of the widespread distribution of cortisol receptors within the inner ear and all auditory pathways up to the cortex (Al-Mana et al., 2008; Kumagami et al., 2013) may lead to interesting findings in cortisol and hearing sensitivity, not just as a cell-protecting hormone.

5. Conclusions

Reduced loudness tolerance is demonstrated during daytime hearing deprivation in contrast to nighttime deprivation; this may be due to increased central gain in an awake cortex. A modest reduction in auditory thresholds was not related to nighttime deprivation. The role of cortisol in hyperacusis cannot be demonstrated in this study, but the study confirms that subjects underwent a normal circadian pattern. Further studies in highly controlled conditions and with the use of neuroimaging may provide an understanding of the central gain and cortical and subcortical neural activity that could be implicated in hyperacusis.

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Declaration of competing interest

None.

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| Table 2 |
|---|
| Significant difference between serum cortisol between Group A and Group B. |
| Cortisol | Group A | Group B | Difference | 95% CI of diff. | t | P value | Summary |
| Serum Cortisol 8AM/4PM | 14.65 | 6.575 | –8.079 | –12.89 to –3.269 | 3.886 | P < 0.001 | *** |
| Serum Cortisol 8PM/4AM | 5.205 | 20.04 | 14.84 | 10.03 to 19.65 | 7.136 | P < 0.001 | *** |
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