Aus dem Biomedizinischen Centrum der Ludwig-Maximilians-Universität München
Lehrstuhl für Physiologische Genomik
Frau Univ. Prof. Dr. Magdalena Götz

Low-frequency sound processing by the human inner ear

Kumulative Habilitationsschrift zu Erlangung der Venia Legendi für das Fach Physiologie

vorgelegt von Dr. rer. nat. Markus Drexl
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1. Summary of the most essential scientific results

Likely a consequence of our society's endeavours to establish sustainable power supplies such as wind farms or heat pumps, anthropogenic sources of low-frequency sound increased in recent years (Moller et al., 2011). At the same time, related or not, complaints from the general public concerning low-frequency sound pollution are becoming more frequent. Since sound is detected by the hair cells of the cochlea, assessing the impact of low-frequency sound on the cochlea should be the first step in all efforts to dissect the chain of events leading to low-frequency sound induced adverse effects.

Sound is considered low-frequency when frequencies are below 100/250 Hz (Berglund et al., 1996). Low-frequency sound, as any other sound, undergoes attenuation through geometric spreading, resulting in a 6-dB decrease in sound pressure level as the distance between source and receiver is doubled. Additional attenuation of the sound pressure level by the atmosphere, however, is frequency-dependent and almost insignificant at low-frequencies (Carlile et al., 2018). As a result, low-frequency sound travels further than high-frequency sound, a fact which can easily be appreciated when listening to loud music from a very distant source. Low-frequency sound also easily penetrates walls and buildings without significant attenuation, which make technical solutions for blocking out low-frequency sound very costly.

Anthropogenic and non-anthropogenic sound sources in our environment are abundant, and can emit sounds with substantial sound pressure levels (Berglund et al., 1996). To understand potential harmful effects of these emissions, a good understanding of how the cochlea processes low-frequency sound is required.

The human auditory system is not well suited to detect low-frequency sounds (Salt & Hullar, 2010), as several mechanisms attenuate the detection during transduction: The middle ear transfer function shows high-pass characteristics and the helicotrema, a small connection between the fluid spaces of Scala Vestibuli and Scala Tympani of the cochlea shunts low-frequency pressure waves, and therefore attenuates the driving force for stereocilia displacement.

The following is a summary of my work concerned with how the human inner ear processes low-frequency sound, and, to a smaller extent, low-frequency electric stimulation.

1.1 Low-frequency acoustic biasing of the human cochlea

Relevant work: Drexl et al. (2012)

There is evidence from animal models (Frank et al., 1996; Frank et al., 1997) as well as from humans (Bian et al., 2007) that very low-frequency sound modulates cochlear activity during sound exposure. Despite the above-mentioned mechanisms attenuating the sound pressure level of low-frequency sound reaching the cochlea, a displacement of basilar membrane will still be caused, with very little phase change between basal and apical positions. This indicates that the basilar membrane, when driven with low-frequency sound, moves almost as one entity along its entire length. Here, I employed distortion product otoacoustic emissions to investigate the effects of low-frequency sound on cochlear mechanics. Otoacoustic emissions are acoustic by-products of active processes in the cochlea and directly reflect the electromotility of outer hair cells. Distortion product otoacoustic emissions are evoked by simultaneously delivering two sinusoidal acoustic stimuli (the primary tone f_1 and f_2) with a fixed frequency ratio f_2 / f_1 of 1.22 at moderate sound pressure levels to the mammalian ear which cause even and odd distortions - new frequency components which are not present in the externally presented tones. These even and odd distortions appear at frequencies which can be accurately predicted by the simple formulae $2f_1$-f_2 (odd) and f_2-f_1 (even). Here, even and odd distortions were evoked in humans during the concurrent presentation of a 30 Hz, 120 dB SPL sinusoidal sound, the biasing tone, and I followed the level of the distortion product otoacoustic emissions as a function of the biasing tone phase. With both distortion types a clear modulation pattern, related to the phase of the biasing tone, could be observed. While modulation patterns of odd distortion product otoacoustic emissions were quite consistent across participants, modulation patterns of even distortion product otoacoustic emissions showed much more individual patterns. My results indicate that intense, low-frequency sound causes a slow, biasing tone phase-dependent operating point shift. The operating point is a discrete point on the transfer function of a system at rest: Here, the transfer function is the relation between the outer hair cell stereocilia deflection and opening probability of outer hair cells transduction channels. Changing the operating point means changing the angle of the mechano-electical transduction-channel containing stereocilia at the apical pole of the hair cells, resulting in an altered opening probability. As a result, distortion-generating mechanisms and consequently distortion product otoacoustic emissions are changed. Distortion product otoacoustic emissions were evoked with frequencies much higher than the biasing tone frequency. Despite the obvious distance between the tonotopic

representations of the primary tones and the biasing tone, the biasing tone still affected the transduction process in a tonotopic region very distant from its own. While my results, along with others, clearly demonstrate that very low-frequency sound affects almost the entire cochlea, and not only the part concerned with low-frequency sound processing at the apex of the cochlea, they also show how different aspects of the cochlear transfer function are altered, as revealed by recording different orders of distortion product otoacoustic emissions.

1.2 The Bounce phenomenon

Relevant work: Drexl et al. (2014); Kugler et al. (2014); Kugler et al. (2015); Drexl, Krause, et al. (2016); Drexl, Otto, et al. (2016); Jeanson et al. (2017); Ueberfuhr, Wiegrebe, et al. (2017)

While low-frequency acoustic biasing (see section 1.1) affects cochlear activity while the stimulus is on, I was also interested in whether intense, low-frequency sound can cause effects which outlast the stimulus duration. Early results can be found in the literature indicating that this is indeed the case: Hirsh & Ward (1952) showed a brief, temporary deterioration of hearing thresholds in humans, occurring after presentation of a loud, long-duration, low frequency (LF) sound, and they coined the term 'Bounce phenomenon' for these events. Later, Kemp (1986) reported that hearing threshold slowly cycled between hyper- and hyposensitivity, and also anecdotally reported effects on cochlear activity. This curious phenomenon was only revisited occasionally over the following decades: Kirk & Patuzzi (1997) and Kirk et al. (1997) showed that the Bounce phenomenon can also manifest itself in measures of cochlear activity such as distortion product otoacoustic emissions and cochlear potentials. I set out to fully characterise the phenomenon in humans: in a comprehensive set of experiments, we followed the hearing threshold, the level of even and odd distortion product otoacoustic emissions and the intensity of an unusual tinnitus percept in the same human participants after the offset of an intense, 30-Hz, 120-dB SPL sinusoidal sound. We found that hearing thresholds slowly changed within a time frame of a few minutes. Monophasic and biphasic combinations of threshold improvement and deterioration occurred, with changes as large as 9 dB. Depending on the test frequency (1,2 and 4 kHz), 59%, 45% and 31% of the participants showed significant changes which lasted, expressed as the median, 179 s, 187 s and 125 s. With a very similar time course, slowly cycling level changes of even order distortion product otoacoustic emissions occurred in 70% of the participants, almost exclusively starting

with an increase, changing over to a decrease and back to baseline in an almost sinusoidal fashion and within a median duration of 192 s. Interestingly, odd order distortion product otoacoustic emissions showed almost no changes, indicating that the transfer function of the mechano-electrical transducer (i.e. the transduction channels situated in the tips of outer hair cell stereocilia) became more asymmetric. All participants also reported a noisy, mostly low-frequency tinnitus percept, which occurred after low-frequency sound stimulation offset. I measured the duration of this tinnitus percept, which had a median duration of 92 s and was thus much shorter than the duration of changes in the other measures, and corresponded roughly to the enhancement phase seen in even order distortion product otoacoustic emissions measurements.

While the frequency composition of the tinnitus percept was not formally characterised in the study mentioned above, participants reported an unusual, short-lived, roaring tinnitus percept, similar to what patients with Ménière's disease report (Havia et al., 2002). Ménière's disease is a chronic disease of the human inner ear, affecting both hearing and the vestibular system, manifesting with hearing loss, vertigo, and tinnitus. In most patients, endolymphatic hydrops can be found, the anatomical correlate of the disease, presenting with a volume increase of the endolymphatic spaces of the inner ear. The pathophysiological mechanisms behind endolymphatic hydrops are unclear, and simplistic models consider a rupture of endolymphatic space boundaries due to the increased volume as the cause for the signs of Ménière's disease (Foster & Breeze, 2013). I suggest some overlap between the mechanisms behind Ménière's disease and the Bounce phenomenon, and it is feasible that both phenomena are the consequence of an ion imbalance of cochlear fluids. As a first step, I characterised the level and frequency of tinnitus in Ménière's disease, and in subjects with the Bounce phenomenon. For this, a matching procedure was developed, which enabled participants to match the level and the frequency content of their tinnitus percept in a semi-automated procedure. Tinnitus levels were lower in Ménière's disease patients than in Bounce subjects. In the Bounce subjects, about half of the participants matched noise to their tinnitus, while the other half chose pure tones below 2 kHz. Ménière's disease patients chose either pure tones with frequencies higher than 3 kHz, or noise. While both tinnitus percepts are unusual, they share not as many characteristics as previously suggested. This might indicate that the Bounce phenomenon and Ménière's disease do not share a common mechanism. It should be pointed out, however, that tinnitus matching is inherently a subjective measure, and participants were non-expert listeners.

The very stereotypic, slow and almost sinusoidal change of cochlear activity observed with the three measures reported above lead me, and others, to believe that the origin of these changes lies in challenging the mechanisms maintaining the ion homeostasis in cochlear fluids. These mechanisms appear to be sluggish and slow, and therefore it takes some time until sensitive conditions are restored after a cochlear insult such as the brief, but intense, low-frequency acoustic stimulation I used here.

In an attempt to achieve a clearer picture of the actual events during the Bounce phenomenon, I employed a technique based on low-frequency biasing of even- and odd-order distortion product otoacoustic emissions (see section 1.1) which enabled me to estimate cochlear transfer functions during the Bounce in human participants. Transfer functions were estimated based on low-frequency biased odd-order distortion product otoacoustic emissions.

The level modulation of the distortion products by low-frequency sound can be mathematically accurately predicted by the second and third derivative of the Boltzmann function, a single, saturating non-linearity representing the mechano-electrical transfer function of the outer hair cells (Lukashkin & Russell, 2005). Since low-frequency sound modulates the level of the emissions, and since a mathematical model of the underlying transfer function is available, I could fit the second and third derivative of this model, respectively, to the recorded modulation patterns and thus obtained the underlying transfer function.

I obtained estimated transfer functions before and after the exposure to low-frequency sound. A clear change of the transfer functions after the exposure was observed, consistent with the suggestion that it is the operating point that slowly cycles away from its resting position, causing the observed effects. As the presence of the primary tones can also cause changes of the operating point, I also explored the effect of low-frequency sound exposure on spontaneous otoacoustic emissions, another product of cochlear amplification processes, which does not require externally presented acoustic stimuli, and, as the name suggest, occurs spontaneously. Spontaneous otoacoustic emissions are typically very stable in both frequency and level over long periods of time (Burns, 2017), and can be considered a real physical sound emission produced by the inner ear. While the mechanisms behind the generation of spontaneous otoacoustic emission are not yet identified in detail, a prevailing view suggests standing waves between the tympanic membrane and a certain cochlear location as the main source of the phenomenon (Shera, 2003). After presentation of low-frequency sound (again 30 Hz, 120 dB SPL for 90 s), the frequency and level of the spontaneous otoacoustic change with a time course very similar to what I, and others, observed before with other measures. Typically, the level and frequency

increased initially, and then slowly decreased before returning to baseline within about 4 minutes. We observed such changes in 56 out of 80 recorded SOAEs, with a median peak-to-trough level change of 6.4 dB (maximum peak-to-trough changes as much as 19 dB) in individuals. Frequency changes were not as pronounced, and were between 2 to 18 Hz. The most important finding here is clearly the fact that the frequency and level changes show the same sign, and not the opposite, as manipulations of middle ear properties would cause (van Dijk et al., 2011).

To characterise the Bounce phenomenon better, it is mandatory to find thresholds for evoking the Bounce phenomenon and to see if there is tuning, i.e. a frequency dependence.

To find the thresholds, we presented a 30 Hz, 90 s sinusoidal stimulus at levels chosen pseudo-randomly from a range between 93 and 120 dB SPL in 3 dB increments. I defined the threshold as the lowest level resulting in a significant level change of spontaneous otoacoustic emissions. Significance was established with a change-detection method, based on a boot-strapping algorithm. The median from 76 estimated thresholds amounted to 102 dB SPL, but in some individuals, 93 dB SPL, the lowest low-frequency sound level employed, sufficed to evoke the Bounce phenomenon. In an attempt to establish frequency dependence, I evoked the Bounce phenomenon with five different frequencies between 30 and 480 Hz in one-octave steps. The level was kept constant at a loudness level of 80 Phons to compensate for the different activation patterns at different frequencies. First of all, the Bounce was largest when SOAE frequency was low, i.e. the tonotopic distance between the SOAE frequency and the Bounce evoking frequency was at a minimum. Regardless the SOAE frequency, the Bounce phenomenon was most pronounced at a Bounce-evoking frequency of 30 Hz, the lowest frequency employed, and increased again at a Bounce-evoking frequency of 480 Hz. This indicates that the size of the Bounce phenomenon is not a simple function of the tonotopic distance between the SOAE frequency and the frequency of the Bounce evoking stimulus. Rather, the Bounce phenomenon decreases as the stimulus frequency increases, suggesting that fewer mechanoelectrical transduction channels are involved. At the highest stimulus frequency, 480 Hz, the effect of ttonotopic distance seems to start to dominate. As sounds with characteristics similar to what I used in this study exist in the environment (Berglund et al., 1996), it is feasible that free-field sound can also trigger the phenomenon.

To test this possibility, I recorded spontaneous otoacoustic emissions in the open ear canal, which makes it possible to use free-field acoustic stimuli to evoke the Bounce. I employed a 30 Hz, 117 dB SPL, sinusoidal stimulus, delivered with loudspeakers, for

90 s. The recorded spontaneous otoacoustic emissions show the very same characteristics as with in-ear stimulation: slowly changing frequency and level within about 4 minutes in almost sinusoidal manner.

At this point, based on the similar time course and the almost sinusoidal changes of the various measures of the Bounce phenomenon, it can be concluded that one and the same mechanism is the source. Patuzzi (2011) suggested, based on theoretical considerations that slow calcium oscillations in outer hair cells are the origin of the Bounce phenomenon. Calcium can regulate the length of outer hair cells, which translates in different deflection angles of the sterocilia, and thus consequently changes the operating point. As a result, the characteristics of the transfer function of the mechano-electrical tranducer are changed, resulting in the typical characteristics of the Bounce phenomenon. Why do calcium levels in outer hair cells become unstable after exposure to low-frequency sound? Intense, low-frequency sound increases the mechano-electrical transduction channel opening probability of a large proportion of outer hair cell, almost along the entire cochlear duct. As a consequence, calcium, along with potassium, will enter the outer hair cells, and trigger calcium-induced calcium release from intracellular calcium stores as well as calcium-induced calcium uptake. If the time constants of these two processes are not equal, oscillations in calcium levels can occur (Patuzzi, 2011).

To test this hypothesis, I tried to interfere with calcium homeostasis whilst evoking the Bounce phenomenon, as measured with spontaneous otoacoustic emissions. A non-invasive way of doing so is the activation of the medial efferent system which innervates the outer hair cells. The medial efferent system can be acoustically activated and is binaural, i.e. contralateral sound activates also the efferent system of the ipsilateral ear. The medial efferent system causes a release of Calcium from intracellular Calcium stores of outer hair cells, thought to regulate outer cell electromotility (Guinan Jr, 2014). I explored the effect of activating the efferent system while evoking the Bounce phenomenon by delivering low-frequency sound (30 Hz, 120 dB SPL, 90s) to the ipsilateral ear, and a broadband sound at 65 and 70 dB SPL to the contralateral ear in order to activate the efferent system. Activating the efferent system shortens the time course of the Bounce phenomenon and reduces amplitude alterations typical for the Bounce phenomenon, which indeed suggest that calcium homeostasis plays a role in the Bounce phenomenon.

1.3 The impact of low-frequency galvanic stimulation on the human inner ear

Relevant work: Ueberfuhr, Braun, et al. (2017)

In a last line of experiments, the effect of low-frequency galvanic stimulation on the inner ear was explored with the aim to achieve a better understanding of the nature of the tinnitus phenomenon associated with the Bounce phenomenon. A bilateral, bipolar mode of galvanic stimulation with the cathode and anode on the mastoid processes was employed. The stimuli consisted of sinusoidal waveforms with a frequency of 2 or 4 Hz at currents between 1 and 4 mA. Here, I explored the impact of low-frequency galvanic stimulation on various psychoacoustic and biophysical phenomena. I found that externally presented, constant-level pure tones were perceived as amplitude-modulated during galvanic stimulation in 16 out of 23 participants. In a second step, I investigated the impact of galvanic stimulation on the Zwicker Tone, an auditory illusion occurring after presentation of notched noise (Zwicker, 1964). 17 out of 22 participants perceived an amplitude modulation when galvanic stimulation was applied during the perception of the Zwicker Tone. Finally, we detected perceived amplitude modulations in the tinnitus phenomenon associated with the Bounce phenomenon during galvanic stimulation in 14 out of 19 participants. Taken together, galvanic stimulation caused a perceived amplitude modulation in 90% of all participants in at least one of the three psychoacoustic measures. Interestingly, no amplitude modulation of distortion product or spontaneous otoacoustic emissions occurred. This leads me to conclude that galvanic stimulation does not affect outer hair cell activity to an extent which could be detected by the measurement of otoacoustic emissions and that the earliest level where interactions between the ascending auditory pathway and galvanic stimulation can occur is the inner hair cell.

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*joint first authors