

APPLICATION 2024

Stiftung Tinnitus & Hören Charité

Research Prize Tinnitus & Hearing

Application title: GABAergic inhibition in tinnitus

Applicant

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Summary

A possible cause of tinnitus is deficient GABAergic inhibition in the brain. This is believed to lead to hyperactivity in the auditory cortex, which results in hearing a sound: tinnitus. For the first time, we apply a PET-scanning technique to measure GABA receptor availability in auditory cortex. Preliminary analysis showed a clear increase of receptor density in humans with tinnitus. Thus, for the first time a biomarker for tinnitus is found with unprecedented robustness. Our preliminary results strongly establish a key role of GABA inhibition in tinnitus, thus motivating further research into pharmacological interventions. The prize of the Stiftung will be used to complete this ground breaking tinnitus study. It will allow us to lay a strong fundament for future work into pharmaceutical interventions for tinnitus.

Introduction

Tinnitus is a phantom sound, often described as a ringing in the ear. Fundamentally, the tinnitus sound must originate in the auditory system. Some neurons there are active when they should in fact be silent. In order to understand the origin of this abnormal activity, it is necessary to look at the chemicals that regulate neuronal activity. These are called neurotransmitters. There are two main neurotransmitters in the brain: Glutamate and GABA. Neurons that release Glutamate trigger an increase of activity in the neurons they are connected with. In contrast, neurons that release GABA tend to decrease the activity of other neurons. Dysfunctional GABA inhibition in the auditory cortex would lead to hyperactivity in that brain area. This would lead to the perception of a sound: tinnitus.

An accumulation of evidence from animal research suggest that tinnitus could be caused by a decrease of GABA levels in the auditory system. All these animal studies point to a crucial role of GABA in the development of tinnitus. Animal studies however do not always produce findings that are consistent with the results of neuroimaging studies in human participants. It is therefore urgent to investigate if inter-individual differences in GABAergic neurotransmission could explain why some humans develop tinnitus and others do not. Our research question is: Is tinnitus in humans related to abnormal GABAergic inhibition in auditory brain areas?

Methods and preliminary results

In a neuroimaging study, we measure both GABA concentration and availability of GABA receptors. This study is performed in people with hearing loss, where we compare participants with tinnitus to those without tinnitus. In our approach, we carefully match the hearing loss and age of participants with and without. The study includes PET scans with a flumazenil tracer, that specifically binds to GABA receptors. A preliminary analysis of the PET scans showed a profound difference between these two groups: in the auditory cortex, the receptor availability is substantially higher for participants with tinnitus compared to those without (See Figure 1). The Research Prize will be fully used to complete this ongoing neuroimaging study.

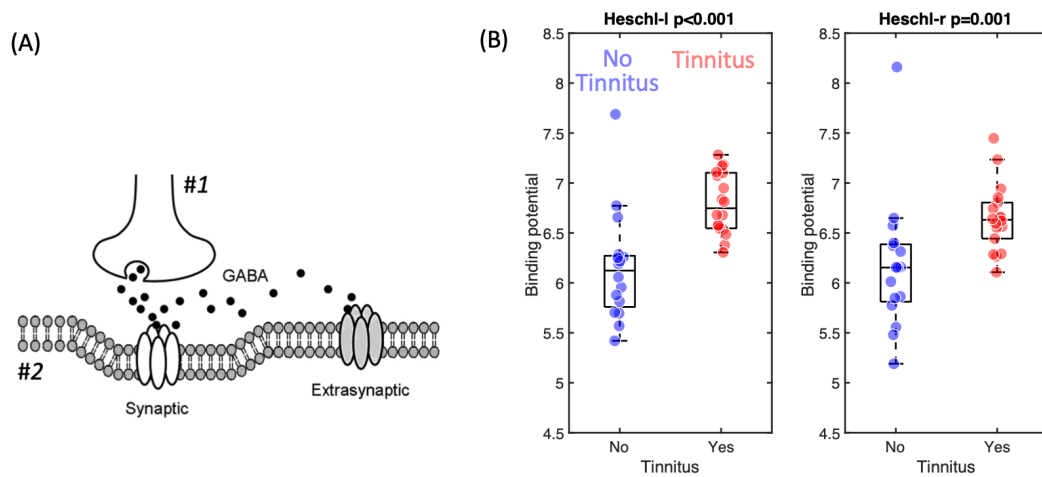


FIGURE 1: (A) Schematic of GABA action in the brain. GABA may be released from neuron #1 into the synaptic space between two neurons. The cell membrane of neuron #2 contains GABA receptors, both synaptic and extrasynaptic. Binding of GABA to a receptor, causes inhibition (reduction) of activity of neuron #2. Impaired function of this GABA inhibition may lead to hyperactivity, which is believed to be at the origin of tinnitus. (B) Preliminary PET scan results. In the PET scans, a flumazenil tracer is injected. The flumazenil molecules bind to unoccupied GABA receptors. Tinnitus (red data points) is associated with a larger receptor availability of GABA receptors. This suggest that there may be too little GABA in the auditory cortex, thus leaving the receptors unoccupied. For the first time, the PET scan technique provides a robust objective measure that differentiates between people with and without tinnitus.

Innovation

This project for the first time applies a PET flumazenil scan technique to tinnitus research. This is possible due to the advanced PET facilities of the University Medical Center Groningen. This work essentially translates results from animal research to humans with tinnitus. The preliminary analysis suggests a key role for GABAergic inhibition is in humans with tinnitus.

Clinical relevance

The key role that we find for GABAergic inhibition in tinnitus, strongly motivates future studies on pharmacological interventions for tinnitus. With new pharmacological techniques (i.e. like small molecules that cross the blood-brain barrier), our results may lead the way towards effective tinnitus interventions. In addition, the preliminary result (Fig 1) suggest that GABA receptor density is a biomarker with unprecedented robustness. For the first time, this objective marker could develop into reliable diagnostic tool to identify tinnitus. This is of great importance for individuals with tinnitus, where our scan technique may be an objective confirmation of the tinnitus complaint. In addition, our scan technique has the potential to develop into a tool for evaluating treatments.

Quality of methodological implementation

In all our neuroimaging work (see also publication list), we carefully match participant groups with respect to hearing loss and age. In this way, we ensure that we identify tinnitus-specific. The GABA imaging study described in this proposal carefully applies these principles. Furthermore, all our research complies with the research code of our institution (<https://umcgresearch.org/w/research-code-umcg>).

Interdisciplinarity

Our research group is a collaboration between physicists, audiologists, psychologists, biologists and medical doctors. Specifically, the research in this proposal includes audiology (Van Dijk, De Kleine), neuroscience (Thioux) and molecular biology (Pyott).