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Chemogenetic Induced Tinnitus Model

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Goals and Objectives:

Some results of this study are sensitive, and will be included in a NEOMED-published manuscript later this year, at which time it will be added to this site. Until then, this is a summary of the topic and general overview of the research.

Tinnitus, or the sensation of ringing in the ears, is a serious neurological condition affecting between 10 and 15% of the population. Risk factors for tinnitus include age and excessive noise exposure. Tinnitus is often associated with other conditions, including insomnia, anxiety, and depression (Faruk et al., 2018). Unfortunately, there are no current FDA approved treatments for tinnitus, possibly due to a lack of reliable animal models for drug screening. Experimental models for tinnitus research are difficult to establish because 1) there is high variability in the success of tinnitus induction techniques in animals; and 2) there is a lack of reliable methods to detect tinnitus in animals. To address the second obstacle, we established the Sound-Based Avoidance Detection (SBAD) method for tinnitus detection in mice (Zuo et al., 2017). In this SBAD method, mice are placed in a shuttle box that is divided at the center by a plastic wall with a single passageway, allowing the mouse to cross between sides. Speakers were installed on top of each side of the shuttle box. By minor electric shocks, experimental mice are trained to cross to the other side of a box when a sound is played (Go trial), and to remain still during silence (No-Go trial). A tinnitus-positive animal is detected when it crosses sides during silence.

The focus of my project is to address the first obstacle by applying chemogenic controlled activation of inferior colliculus (IC) to establish a new tinnitus model. The IC is one major processing center in central auditory pathway, and its abnormal activation is highly implicated in tinnitus (Kaltenbach and McCaslin, 1996). A majority of previous studies have found varying degrees of correlation between tinnitus and increased spontaneous firing within the IC after cochlear deafferentation, although other studies reported no change in firing rates (Brozoski et al., 2012). These discrepancies could be for a number of reasons, including the aforementioned difficulty in tinnitus detection, and the often-variable timeline of tinnitus development.

Recently, neuronal activity can be controlled by designer receptors exclusively activated by designer drugs (DREADD) (Roth, 2016). These DREADDs use G protein-led receptors that respond exclusively to Clozapine N-oxide (CNO), a modified chemical compound from an antipsychotic drug. Here, I applied this chemogenetic method to activate IC excitatory neurons, and determine that this activation could lead to a reliable and efficient tinnitus model for future translational studies.