

Pre-Clinical Animal Trials to Assess the Efficacy of NMDA and Kappa-Opioid Receptor Antagonists in Treatment of Tinnitus

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Our proposal is based on preliminary studies that show round window noise (RWN), a measure of auditory nerve activity associated with salicylate (SA)-induced tinnitus, is reduced with two different therapeutic agents, Gacyclidine (GA) a NMDA receptor antagonist and nor-Binaltorphimine (nor-BNI) a kappa-opioid receptor antagonist. Neither agent affected cochlear sensitivity. These exciting results raise the potential of therapeutic interventions in human. There are several questions, however, that must be addressed in pre-clinical trials in an animal model, before moving to clinical trials, these are the goal of our proposed studies. Specific Aim 1 is to match our physiological metric of tinnitus (RWN) with the perception of tinnitus tested using the gap-detection startle reflex. We hypothesize that reduction of RWN by GA and nor-BNI in the SA tinnitus model will be accompanied by amelioration of the perception of tinnitus.

It is important to match a treatment to the specific type of tinnitus it can help. Specific Aim 2 will test the hypothesis that treatment with GA and nor-BNI will reduce the perception of tinnitus when it is associated with increased RWN and not when the perception occurs without increased RWN (central tinnitus). We will compare the efficacy of our treatments in two different tinnitus models: SA-induced (with increased round window noise) versus noise-induced (without increase in round window noise).

If GA and nor-BNI achieve their effects through different mechanisms, combining them may be even more effective. Specific Aim 3 tests the hypothesis that there will be synergy when GA and nor-BNI treatment of tinnitus are combined.

Specific Aim 4 tests safe limits, by comparing the efficacy (RWN and gap-detection startle reflex) and safety (histopathology of hair cells and auditory nerve) with different dosages of GA and nor-BNI or both together.

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