GAP DETECTION AS A HIGH THROUGHPUT, OBJECTIVE BEHAVIORAL SCREEN FOR TINNITUS

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Despite the prevalence of tinnitus and the debilitating symptoms in many patients, the cause(s) and underlying mechanisms of tinnitus remain unknown. As a result, prevention and treatment options for tinnitus have been slow to develop. One reason for the relatively slow progress in tinnitus research is the inherent difficulty in measuring tinnitus in an animal model. While human tinnitus researchers can rely on the subjective descriptions of their patients, animal researchers are not so fortunate. The basic question addressed by the current study is this: How can one get a laboratory animal to “tell” when it has ringing in the ears and what that ringing sounds like?

Here we attempted to address that question by proposing a new approach to testing tinnitus that does not require the weeks or months of training required in some other models, requires no food or water deprivation, no electric shock and uses equipment that is commercially available to researchers. The approach makes use of the acoustic startle reflex and its inhibition by preceding stimuli. When an abrupt noise pulse is presented to a freely behaving rat it will reflexively startle. If, however, the startle-eliciting noise pulse is preceded in time (by about 100 ms) by any noticeable change in the sensory environment, such as a gap in the background sound or the presentation of any audible sound, the change in the sound environment will serve to inhibit the subsequent startle reflex. This procedure is generally known as prepulse inhibition of the startle reflex and the phenomenon has been used for decades in humans and laboratory animals alike to assess which pre-stimuli an animal is able to effectively process. In the studies summarized here, we adapted the prepulse inhibition setup by placing a constant background noise in the testing chamber and removing the background momentarily before the startle stimulus, producing a silent gap in the background. The presence of the silent gap in normal control animals typically serves as a strong inhibitory signal to depress the startle reflex, cutting the reflex amplitude by at least half. To adapt this test for tinnitus, we hypothesized that if the background sound present in the testing chamber sounded like the animals tinnitus, the rat would have difficulty hearing the silent gap and less inhibition of the startle might be expected. Essentially, animals with tinnitus would continue to hear the background sound during the silent gap. Here we present a summary of recent findings suggesting that this test is sensitive to both salicylate-induced tinnitus as well as chronic tinnitus developing after noise exposure. As predicted, animals with prior evidence of tinnitus exhibited deficits detecting silence when the background sound was similar to their suspected tinnitus. This method has been cross validated with both the operant lever pressing technique of Bauer &

Brozoski as well as the polydipsia method of Salvi et al. These results support the hypothesis that an animal with tinnitus will show impaired gap detection in an acoustic environment with features resembling its tinnitus. We interpret these data to indicate that animals with tinnitus continue to hear a signal (tinnitus) during the "silent" gap. The frequency selectivity of the findings (deficits at frequencies similar to their suspected tinnitus and normal responses when the background sounds are explicitly different from their suspected tinnitus frequencies) further suggest that worse gap detection cannot easily be explained by either hearing loss or generally degraded performance. Several additional controls for hearing loss are also described that help rule out hearing loss as an explanation for the deficits seen in animals with suspected tinnitus. Overall, these results suggest a new rapid (~40 min) behavioral screening method for tinnitus in individual animals that requires no prior training or preparation. Additionally, up to 8 animals can be tested for tinnitus simultaneously with the present equipment, making it possible to do high throughput screening for tinnitus. The high throughput screening potential of the current gap detection testing for tinnitus could help advance our understanding of the underlying mechanisms of tinnitus and expedite the development of new prevention and treatment strategies for this common and sometimes debilitating condition. Finally, because startle reflex methodology has also been used extensively in humans, these data suggest that similar gap detection deficits might be present in humans with tinnitus. If such a deficit were to be found in humans as well, it would suggest the possibility, for the first time, of a rapid, objective measure of what has always been a subjective condition in humans.