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Nerve Simulation Paired With Tones May Improve Tinnitus

BY JEFF EVANS

FROM NATURE

A therapeutic strategy for tinnitus that increases the number of auditory cortical neurons tuned to frequencies other than the one causing the condition has shown promising results in a rat model of the disorder.

By pairing a range of tone frequencies with peripheral stimulation of the vagus nerve, Navzer D. Engineer, Ph.D., and his associates at the University of Texas at Dallas reversed the physiological and behavioral correlates of tinnitus in noise-exposed rats.

Temporary relief of tinnitus symptoms in humans has been observed with the use of sensory exposure or discrimination training to reverse changes in the organization of the auditory cortex, but Dr. Engineer and his colleagues found that their approach may generate long-term effects.

In rats exposed to 1 hour of 115-dB, octave-band noise centered at 16 kHz, microelectrode recordings of neurons in the primary auditory cortex showed increases in the number of sites that were tuned to frequencies between 2 and 4 kHz, as well as neuronal changes in frequency tuning and synchronization. All of these changes are "similar to the physiological changes observed after noise exposure that have been proposed to be directly responsible for tinnitus," according to the investigators (Nature 2011;470:101-4).

These rats could not detect a gap in narrowband noise centered on 8 or 10 kHz, but they could detect a gap in noise when it occurred in narrowband noise centered on 2 or 4 kHz or in broadband noise. Because it is impossible to know the subjective experience of rats exposed to this level of noise, Dr. Engineer and his colleagues used this impairment in gap detection to signify that they are experiencing a mid-frequency tinnitus that fills the silent gaps, as other studies have done.

The degree of gap impairment seen in the rats was significantly correlated with the number of sites in the primary auditory cortex that had changes in frequency tuning and their relative change in frequency bandwidth.

To verify that these correlations were not the result of variability in initial cochlear trauma, the investigators treated the rats with impaired gap detection at 8-10 kHz by administering VNS in combination with randomly interleaved pure tones that span the rat hearing range (except for tones at frequencies of 8-10 kHz). After 10 days of therapy, these rats could detect gaps in the putative tinnitus frequency of 8-10 kHz up to 3 weeks later. These results make the pairing of VNS with multiple tone frequencies "the first method reported to generate a long-lasting reversal of a behavioral correlate of chronic tinnitus," the investigators wrote.

After 3 weeks of therapy, most of the properties of the rats' primary auditory cortex returned to normal levels. Based on these preclinical results, a clinical trial with a wireless VNS device will begin in Europe later this year, according to Dr. Engineer.

MicroTransponder Inc., a medical device company affiliated with the University of Texas at Dallas, funded the research and the upcoming clinical trial. Other research support came from the James S. McDonnell Foundation, the Texas Advanced Research Program, and the National Institute on Deafness and Other Communication Disorders. Dr. Engineer is an employee of MicroTransponder Inc. Coauthor Michael P. Kilgard is a consultant and shareholder of MicroTransponder Inc. ■

ADVISER'S VIEWPOINT

Novel Approach for a Persistent Problem

Central sensitization is defined as the augmentation of normal cortical responsiveness to sensory input. Sensitization is thought to arise from neuronal plasticity induced by excitatory stimulation, inflammation, or injury. Through changes in synaptic connectivity, membrane excitability, and reduced inhibitory controls, a state of sustained neuronal hyperexcitability is created. Central sensitization is a proposed etiology of tinnitus, fibromyalgia, headache, and other chronic pain syndromes. These have traditionally been considered "medically unexplained" and share challenges in diagnosis and management. Tinnitus provides a good case study for these difficulties.

Tinnitus affects millions of people, with symptoms ranging from mildly disturbing to significant disability with disturbed sleep, concentration, mood, and even suicide. There is no uniformly accepted diagnostic paradigm. Tinnitus can accompany sensorineural hearing loss, but a hearing test does not confirm or quantify the degree of subjective symptomatology. Treatment is also not standardized or strongly evidence based. Common interventions include hearing aids, masking devices, habituation or cognitive behavioral therapy, antidepressants, and anxiolytics. Many patients struggle to find relief.

If neuronal plasticity can cause tinnitus and chronic pain, could it also be used to "desensitize" altered cortex as a cure for these disorders? Preliminary studies have suggested that transcranial magnetic stimulation may induce at least short-term change in central sensitization, but long-term outcomes are not yet known. Dr. Engineer and his colleagues have now taken a novel approach to inducing changes in cortical hyperexcitability by indirect, peripheral stimulation of the vagus nerve. In a rat model of tinnitus, they demonstrated that vagal stimulation in conjunction with paired tone exposure led to a sustained changes in auditory cortical activity and synchronization. The study serves as initial proof of concept for the ability of vagal stimulation to induce changes in neuronal plasticity.

The means to safely, chronically stimulate the vagus nerve in humans is already available. Demonstrated efficacy of the vagus nerve stimulator (VNS) for refractory partial epilepsy, although by mechanisms unproven, suggests VNS can alter cortical excitability in humans. Much remains to be determined, however, before VNS is proven as a clinical treatment for tinnitus or chronic pain. Future studies will need to address not only clinical efficacy, but also appropriate patient selection, treatment paradigm, and cost effectiveness. Nevertheless, the study conducted by Dr. Engineer and his associates offers early promise for a potentially novel intervention for these disabling conditions that often elude our current best efforts at management.

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Herpes Zoster Vaccine Proves Effective in Real World

BY MARY ANN MOON

FROM JAMA

The herpes zoster vaccine reduced the incidence of the disease by 55% in real-world clinical practice, according to a recent report.

This finding, from a retrospective cohort study involving more than 303,000 healthy, community-dwelling adults aged 60 and older from diverse backgrounds, confirms and extends the results of clinical trials that found the vaccine effective under idealized conditions.

The cohort study found further benefits that had not been shown before: The herpes zoster vaccine also decreased the rate of ophthalmic herpes, and it was effective in patients with underlying chronic diseases that were feared to interfere with their immune function.

Thus, the benefits of the herpes zoster vaccine extend to the ophthalmic manifestation of the disease, to all races, both genders, and all ages over 60, as well as to patients with chronic illness, said Hung Fu Tseng, Ph.D., of Southern California Kaiser Permanente, Pasadena, and associates.

These results are particularly important given that the public's acceptance of the vaccine has been slow and it is not yet in widespread use. "This vaccine has the potential to annually prevent tens of thousands of cases of herpes zoster and postherpetic neuralgia nationally. To date, herpes zoster vaccine uptake has been poor due to weaknesses in the adult vaccine infrastructure and serious barriers to the vaccine among clinicians and patients.

They assessed the vaccine's effectiveness in 75,761 California patients in the managed care plan who were immunized in 2007-2009, comparing outcomes with those of 227,283 age-matched control subjects who were not vaccinated. A total of 5,434 cases of herpes zoster developed during an average follow-up of 1-2 years.

The incidence of herpes zoster was 6.4 per 1,000 person-years in the vaccinated group, compared with 13 per 1,000 patient-years in the control group. This reflects a 55% reduction in incidence with the vaccine, the investigators wrote. This result showed that "1 episode of herpes zoster would be averted for every 71 patients" vaccinated, they wrote (JAMA 2011;305:160-6).

The vaccine benefit persisted across all subgroups of patients, particularly in the oldest subjects. "Our results support recommendations to offer herpes zoster vaccine to eligible patients of all ages, including the oldest population," Dr. Tseng and his associates wrote.

"For the oldest group, this could translate into a very large absolute reduction in disease because they bear the greatest burden of herpes zoster and postherpetic neuralgia," the researchers added.

Effectiveness against ophthalmic herpes is an important finding not reported previously. Ophthalmic involvement is common and can lead to serious vision-threatening sequelae, they noted.

The finding that the vaccine also was effective in patients with chronic underlying disease was "reassuring," because "these diseases might have interfered with functional immunity and vaccine effectiveness. Control of pain from herpes zoster and postherpetic neuralgia is complicated in these patients because of their underlying conditions and the medications they must take," the authors wrote.

The study involved only fully insured patients in a single region of the country, limiting its generalizability. ■