Review

Deep Brain Stimulation—A new treatment for tinnitus

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Abstract Intractable tinnitus can lead to serious consequences. Study evidence indicates that the central nervous system is involved in generation and maintenance of chronic tinnitus and that tinnitus and other neurologic symptoms such as chronic pain may share similar mechanisms. Brain ablation and stimulation are used to treat chronic pain with success. Recent studies showed that ablation and stimulation in non-auditory areas resulted in tinnitus improvement. Deep brain stimulation (DBS) may be an alternative treatment for intractable tinnitus and deserves further study.

Key words tinnitus; deep brain stimulation; electrical stimulation

Introduction

Prevalence of tinnitus among general population has been reported to be between 13 and 18.6% in most studies [1-3]. The prevalence of current tinnitus in US general population from the 1987 Health Interview Survey is relatively low at 2.7% [4]. The prevalence increases in older people, in people with poor health and in people with hearing disorders [4-8]. Acoustic therapy, counseling and certain medications provide some relief for most tinnitus patients, but often fail in patients with severe tinnitus. Suicide has been reported in patients with severe tinnitus[9, 10].

Acoustic therapy uses external sounds and remains the mainstay of tinnitus management[11-13]. Contemporary acoustic therapy also includes intensive psychological intervention, aiming at long- term relief through habituation [14,15]. Although widely practiced, acoustic therapy remains ineffective in as many as 20% of patients with severe tinnitus[15].

Lidocaine reduces tinnitus perception, but its administration and side effects limit its clinical utility [16]. Alprazolam has been shown to reduce tinnitus loudness and help patients sleep[17]. Nortriptyline helps tinnitus patients cope with tinnitus- related mood problems, reduces tinnitus loudness [18,19].

Several tinnitus treatment efforts have used electrical stimulation. Transcutaneous and transcochlear electrical stimulation have produced different, sometimes conflicting results, reducing tinnitus in some patients [20-24]. Cochlear implants in patients with profound hearing loss often result in decreased tinnitus perception [25, 26]. Transcranial magnetic stimulation is currently being studied for its potential in providing tinnitus relief with some promising results[27-29].

Effects of other reported tinnitus treatments are not conclusive, although some are used as adjuncts to acoustic and pharmacological therapies.

Tinnitus mechanisms

Tinnitus mechanisms involve both peripheral and central auditory systems. Damage to the cochlea causes hearing loss and often triggers tinnitus, but the central nervous system (CNS) is likely to play a key part in chronic tinnitus.

Acoustic signals are encoded in nerve firing patterns along the central auditory pathways[30], and certain patterns represent "silence" [31]. Non-auditory systems participate in interpretation of auditory signals[31-33], producing emotional and autonomic responses. Random spontaneous discharges normally exist along the audito-

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ry pathway in silence[30]. Such activity may provide inhibition for higher level structures[34], necessary in maintaining normal excitability. Damage to peripheral auditory organs produces abnormally synchronized discharges in the auditory nerve. Synchronized activities, in contrast to the normal random spontaneous activity, have been proposed as a cause of phantom auditory sensation [31, 35]. Loss of spontaneous discharges may also reduce normal inhibition, causing an excitatory/inhibitory imbalance, altered excitability and changes in discharge patterns in auditory nuclei. The result may be false sensations of sound resulting in tinnitus.

Jastreboff proposed multi-stage processing by the CNS in chronic tinnitus, including detection, perception, evaluation of and reaction to tinnitus patterns [32, 33]. A variety of central activities involving auditory and non-auditory systems take place in tinnitus, which enhance the detection process and induce non-auditory responses. The neural activities related to tinnitus may be weak, but the associated non-auditory neural activity causes systemic responses beyond what would be expected in response to an equivalent external sound[31]. Interaction between different neural centers may form oscillatory or reverberant patterns that are self-perpetuating and produce lasting tinnitus[36]. The "code of silence" is thus replaced by the tinnitus "code".

Perception of abnormal activity within the auditory pathways is different from that evoked by external sound [32]. Direct electrical stimulation of auditory structures induces perceptions that resemble tinnitus, rather than external sound [37]. In animal and human studies, a component near 200 Hz in the spectra of ensemble spontaneous activity is often present in the absence of acoustic stimulation when factors known to cause tinnitus are introduced. This component can be eliminated by lidocaine[38-40]. These evidences suggest that alteration of neuroelectrical activity in the CNS is important in tinnitus generation. Disrupting abnormal activities shouldl change tinnitus perception and potentially result in tinnitus relief.

Deep brain stimulation for tinnitus

Effective treatments are needed for intractable tinnitus. Deep brain stimulation (DBS) has been used in treating a variety of CNS disorders including movement disorders and chronic pain. When treating movement disorders or chronic pain, the target of DBS is usually the motor or sensory nuclei in the thalamic area[41, 42]. The effectiveness of DBS in treating movement disorders has been established. It has also been shown to be effective in controlling chronic pain in selected patients [43-45].

Mechanisms of DBS treatment for chronic pain and movement disorders

Extensive and complicated connections and feedback loops exist in somatosensory pathways. Central activity is constantly modulated by peripheral input. Loss of peripheral input causes changes in central activity, such as increased discharge rates of neurons in thalamic nuclei[46, 47]. Altered central neural activity patterns are seen following a prolonged course of chronic pain, including memory-like, reverberating activities that can be interrupted by electrical stimulation[48].

Normal motor functions are maintained by balanced inhibitory and excitatory activities among nuclei in the basal ganglia and other related structures. Failure of the sophisticated and delicate balance results in movement disorders[49, 50].

Both ablation and stimulation in the thalamus change neural activity patterns in relevant nuclei, restoring excitatory/inhibitory balances, and have been used for chronic pain and movement disorders. As imaging and stereotactic guidance technologies improve, the procedures continue to gain wider acceptance with increasingly satisfactory results[51]. While both ablation and DBS procedures are associated with low rate of complications, DBS stimulus parameters can be modified to counteract decrease in treatment effects.

Similarities between tinnitus and chronic pain

Similarities between tinnitus and chronic pain include: 1) They are subjective sensations, 2) Sectioning of afferent nerves is not consistently helpful, 3) The CNS is involved in their generation and maintenance, and 4) Peripheral stimulation, electrical for pain and acoustic for tinnitus, provides relief for some patients. Moller and Tonndorf compared tinnitus with chronic pain [52, 53]. Moller concluded that, as in pain, hyperactivity or hypersensitivity of certain neuronal centers is an important mechanism for tinnitus and that new tinnitus treatments might develop from experiences with management of chronic pain[52].

Assuming that mechanisms involved in chronic pain are related to that of tinnitus, it follows that similar treatment principles can be applied in tinnitus. Auditory sensation has been reported during DBS procedures for movement disorders[54], indicating that DBS can modify auditory function.

Why DBS should work for tinnitus?

One way to change the patient's tinnitus perception may be to disrupt patterns of tinnitus-related activities. As with other sensory pathways, the thalamus is an important structure where auditory nuclei (the medial geniculate body, MGB) are present and form complex connections. Although tinnitus-related neural activities in the MGB have not been studied, altered activity patterns related to tinnitus have been identified in brainstem level auditory nuclei [55-57]. It is conceivable that such activities will be relayed to the auditory cortex, hence producing tinnitus perception, via the MGB in the thalamus. Disrupting tinnitus-related activities in the auditory nuclei at the thalamus level therefore has the potential to alter patient's tinnitus perception.

Jeanmonod et al reported improvement in 3 of 6 tinnitus patients treated with ablative procedures performed in the medial thalamus[58]. In his study, which included patients having neurogenic pain, movement disorders, epilepsy and tinnitus, 45% of the 2012 medial thalamic single units investigated showed low-threshold calcium spike bursts activity. He proposed that a self-perpetuating thalamic cell membrane hyperpolarization was the common mechanism for these treatment-resistant neurologic symptoms.

Electrical stimulation of peripheral auditory organs produces tinnitus relief in some patients. Tinnitus relief has also been reported in patients who have received cochlear prostheses or brain stem implants[25, 26, 59]. Such relief probably comes from altered activity patterns in auditory pathways by electrical stimulation. Stimulation of more central auditory structures may also provide tinnitus relief through breaking the proposed reverberating patterns responsible for chronic tinnitus [36].

In a preliminary study by the authors[60], 3 of the 7 patients with tinnitus who received DBS treatment for movement disorders reported tinnitus reduction by DBS. The effectiveness is similar to ablation reported by Jeanmonod et al. (3 of 6 subjects reported tinnitus improvement). It is interesting that ablation and stimulation of non-auditory structures modified tinnitus perception. This implies that tinnitus perception can be mediated by non-auditory as well as auditory structures and that the success of DBS for tinnitus relief is not strictly limited to targeting auditory structures, although auditory structures would seem to be the targets of choice for most effective stimulation.

Where to stimulate?

In a preliminary study by the authors, DBS devices were implanted for movement disorders and stimulation was applied to the ventral intermedius nuclei in the thalamus. Hypothetically, DBS for tinnitus would be most effective when applied to neurons along the auditory pathway. Research data have suggested altered activity patterns in the inferior colliculus and dorsal cochlear nucleus in animal tinnitus models. However, these structures may be difficult to reach through established sterotactic DBS approaches. Complications at brainstem level may also pose a risk of severe sequelae that can be life-threatening. DBS in the thalamus region is an established approach and widely practiced at neurosurgical centers. The auditory nucleus in the thalamus is the MGB. Placement of DBS electrode in the MGB or its vicinity may potentially provide maximal effects in altering neural activity patterns in this section of the auditory pathway and in affecting tinnitus perception. How stimulating the MGB would affect hearing is an unanswered question.

Alternatively, it is also possible that stimulation of non-auditory structures may provide similar benefits. Tinnitus was reduced in nearly half of the patients studied in the authors' preliminary study in which DBS devices were implanted in the ventral intermedius nucleus, a non-auditory structure. Studies on somatotinnitus have suggested cross-modality mechanisms in tinnitus generation [61, 62]. It is possible that stimulation of non-auditory structures may affect tinnitus perception through this mechanism, without generating auditory side effects.

It is also possible that suppression of tinnitus and effects on hearing by DBS will be determined by a combination of electrode location and stimulus parameter settings. Clearly, there is a lack of information in this area.

What stimulus parameters may be appropriate?

DBS for movement disorders and pain commonly uses pulses of square waves. Typical pulse width is in the range of 90 to 210 μs and stimulus amplitudes are generally between 1 and 3 volts. The rate of stimulation is frequently set at 185 pps (pulse per second). These combinations appear to provide symptom relief for most patients with movement disorders or chronic pain and have been shown to be safe in most cases. It is possible to modify these parameters to regain benefits should there be tolerance and symptom recurrence. These parameter combinations have demonstrated efficacy in suppressing tinnitus in nearly half of the patients in our preliminary study with DBS. Since no parameter manipulation was implemented during that study, it is not clear if parameter combinations other than the ones listed above would provide different results. It is perceivable that positioning of DBS electrode may affect parameter combinations required for tinnitus relief. A stimulus electrode located near auditory structures may require a different stimulus parameter combination regimen to maximize its effects on tinnitus while minimizing potential side effects (i.e., altered auditory or somatic sensations and disrupted motor functions).

Patient selection

For movement disorders and chronic pain, DBS is recommended for patients who have failed pharmacological and other treatment options. While generally safe, DBS is a surgical procedure and is associated with certain rates of complications and side effects. For a non-life-threatening condition such as chronic tinnitus, benefits have to be weighed against potential risks. It can be envisioned that DBS will be restricted to patients, whose severe tinnitus significantly affects their life qualities and who have not been able to benefit from all other available treatment options. Psychiatric stability may be an important indication criterion.

Potential risks

DBS procedures are relatively safe and well-tolerated. Complications include bleeding, infection, and CSF leak, and typically happen at a rate lower than 6% [63-65]. Side effects may include ataxia, dysarthria, and gait disturbance and are generally reversible by adjusting stimulus parameters [66, 67]. Psychiatric side effects have been reported, including depression, mania, aggression, and deficits in language[68]. Hardware failure occurs at a rate between 7 to 26% [69-71], sometimes resulting in extraction or replacement. When implanted to control tinnitus, it is possible that stimulation may affect auditory perception, sensory and motor functions. Because these procedures are typically done under sedation and local anesthesia, and the patient stays awake throughout the process, most of these complications can be identified, and hopefully avoided. Apparently, questions regarding safe application of DBS in tinnitus patients, as well as its efficacy, can only be addressed in a clinical trial study involving an appropriate size sample of patients.

Summary

DBS is a promising technique for the treatment of severe tinnitus. It is effective in controlling symptoms in other similar treatment-resistant neurological disorders. Patient selection criteria, electrode location and stimulus parameters must be established.

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