Therapeutic Potential of Neurotrophin Gene Therapy in Noise-Induced Hearing Loss and Age-Related Neural Hearing Disorders

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Abstract

Neurotrophin (NT) cochlear gene therapy might perhaps give a single treatment that might greatly enhance neuronal survival, resulting in CI patients, provided the many challenges described above can be adequately addressed and safety concerns allayed by more animal model investigations. This is particularly crucial for juvenile CI patients, who have to rely on electrical hearing for the remainder of their lives, and whose outcomes are quite different. In addition, NT gene therapy may have the potential to treat patients with noise-induced hearing loss or neural presbyacusis (e.g., age-related cochlear synaptopathy), where primary neuronal loss is a key cause of hearing loss. Animal research into noise-induced hearing loss has shown that even exposures that generate only reversible threshold alterations and no hair cell loss can lead to permanent loss of SGN synapses on hair cells, resulting in functional impairments and ultimately SGN degeneration. Cochlear synapses frequently precede both hair cell loss and threshold increases in human ears, according to current studies. Cochlear synaptopathy is characterized by ears with intact hair cell populations and normal audiograms as "hidden" hearing loss. Many frequent perceptual abnormalities, including speech-in-noise difficulties, tinnitus, and hyperacusis, are likely produced by suppressing affected neurons, which radically alters information processing. Thus, in the future, NT gene therapy may be successful in inducing SGN peripheral axon resprouting and synaptic regeneration into residual (or even regenerated) hair cell populations. We have demonstrated compelling evidence that, in this investigation, BDNF gene therapy can boost SGN survival and enhance peripheral axon maintenance or rerouting. NT-3 has been found in adult animals exposed to acoustic damage to induce synaptic regeneration of these fibers, reconnecting them to hair cells and their ribbon synapses, and restoring hearing function. Combining BDNF and NT-3 gene therapy may be the most effective way to maintain/restore a more normal cochlear neuronal substrate.

1. Introduction

Hearing loss frequently has negative educational, social, and vocational repercussions that have a substantial impact on one's quality of life. Furthermore, hearing loss is linked to cognitive impairment (Chern and Golub, 2019) and depression (Jayakody et al., 2018), particularly in the elderly. Although gene therapy options detailed in earlier papers in this Special Issue may improve these numbers in the future, for severe to profound hearing loss, the cochlear implant (CI) is now the standard of care. In general, today's CIs are quite successful. The average CI recipient utilizing the most up-to-date technology gets roughly 80% of high-context sentences right through voice recognition and can use a phone (Zeng et al., 2008). Music may even be enjoyed by the affluent (Drennan and Rubinstein, 2008; Won et al., 2010; Jiam et al., 2019). However, there is still a lot of variation in results among individual CI receivers (Firszt et al., 2004; Holden et al., 2013), especially in young people (Svirsky et al., 2000; Ortmann et al., 2017; Zhao et al., 2019), and many CI users get little or no benefit. The amount of surviving cochlear SGNs in individual CI recipients has been demonstrated to be a major factor determining performance, and this variability is likely connected to variances in auditory nerve survival (Kamakura and Nadol, 2016; Seyyedi et al., 2014). Furthermore, there is research that has found links between indirect functional markers of neural survival and CI results (Holden et al., 2013; Scheperle, 2017; Schvarts-Leyzac and Pfingst, 2018), bolstering the case for auditory nerve survival. As a result, there has been a lot of interest in recent years in looking into possible therapeutics for improving auditory nerve survival by slowing SGN degeneration following deafness. Osmotic pumps and other techniques have been employed in deafened animal models to administer a number of NTs directly to the cochlea in preclinical research, and the results have been encouraging, particularly with BDNF. However, due to concerns regarding infection and effectiveness duration, osmotic pumps are not a good alternative for extensive clinical use, and other techniques are not yet completely established (see Ma et al., 2019 for review). Recent research has focused on the idea of employing neurotrophin gene therapy to drive NT expression by cochlear target cells. This might pave the way for a one-time therapy that promotes long-term NT expression and better SGN survival following deafness.

This review first describes the data supporting exogenous NTs' effectiveness in supporting enhanced SGN survival within the cochlea following hearing loss in this review. We'll also go over the animal research that's been done so far with NT gene therapy in the inner ear and other non-auditory uses. Finally, we'll go through some of the remaining concerns, such as optimum vector selection, treatment schedule, and delivery location/method, among other things. Prior to contemplating clinical application, this must be settled.

Exogenous neurotrophins increase SGN survival following deafness.
Over the last two decades, there has been a lot of interest in neurotrophic drugs that might promote SGN and auditory nerve survival and so improve CI results (see Staecker et al., 2010; Leake et al., 2013). The NTs, which are members of the nerve growth factor (NGF) family of proteins and comprise NGF, BDNF, neurotrophin-3 (NT-3) and NF-4/5, each of which binds to distinct high-affinity Trk family receptors, are of special importance. BDNF and NT-3, in particular, are known to play critical roles in SGN formation and maintenance. Neurotrophins control neuronal differentiation and survival throughout cochlear development (Farinas et al., 2001; Fritzsch et al., 1999; Rubel and Fritzsch, 2002; Yang et al., 2011). Hair cells, supporting cells of the organ of Corti, and neurons of the cochlear nucleus all offer neurotrophic support to SGNs (Fritzsch et al., 1999; Schecterson and Bothwell, 1994; Stankovic et al., 2004), and SGNs express the BDNF (TrkB) and NT-3 (TrkC) receptors (Schecterson and Bothwell, 1994; Ylikoski et al., 1993). Furthermore, BDNF and TrkB have recently been discovered in the developing human cochlea, indicating that they have a comparable role in SGNs in humans (Johnson Chacko et al., 2017)
Both BDNF and NT-3 are involved in the maintenance of SGNs in the adult cochlea (Qun et al., 1999; Ylikoski et al., 1993), and the loss of this neurotrophic support after deafness leads to SGN degeneration via apoptotic cell death (Alam et al., 2007; Fritzsch et al., 1999). Furthermore, multiple investigations have shown that exogenous NTs administered directly to the cochlea through an osmotic pump over a period of weeks can preserve SGNs and enhance neuronal survival following deafness caused by different stressors (Ramekers et al., 2012; Leake et al., 2013; Ma et al., 2019). Deafened guinea pigs (Agterberg et al., 2008; Glueckert et al., 2008; Miller et al., 2007; Shepherd et al., 2008; Wise et al., 2005; Ramekers et al., 2015) and neonatally deafened cats (Agterberg et al., 2008; Glueckert et al., 2008; Miller (Leake et al., 2011). Other NTs, such as glial-cell-line-derived neurotrophic factor (GDNF) (Kanzaki et al., 2002; Maruyama et al., 2008; Yagi et al., 2000; Ylikoski et al., 1998) and Fibroblast growth factor (FGF), have been shown to have neurotrophic effects (Glueckert et al., 2008). Furthermore, while one study (Gillespie et al., 2003) reported rapid SGN loss after NT delivery was stopped, several other more recent studies (Agterberg et al., 2009; Leake et al., 2011; Shepherd et al., 2008) have shown that neurotrophic effects can last long after exogenous NT delivery is stopped (Agterberg et al., 2009; Leake et al., 2011; Shepherd e (Shepherd et al., 2005; Leake et al., 2013). Importantly, when BDNF infusion was paired with CI implantation, a highly significant increase in SGN survival (>50 percent increase re: contralateral) was sustained when electrical stimulation from the CI was sustained 3–4 months after BDNF supply was stopped (Leake et al., 2013).
Exogenous NT infusion has been shown in several labs to enhance the survival of radial nerve fibers in the osseous spiral lamina (the peripheral dendrites of the SGNs) as compared to deafened controls (Glueckert et al., 2008; Leake et al., 2011, 2013; Pettingill et al., 2007; Wise et al., 2005). Reduced thresholds and higher dynamic ranges for electrical stimulation provided by CI were related to improved fiber survival (Leake et al., 2013; Landry et al., 2013), which might enhance CI performance. BDNF injection, on the other hand, frequently results in widespread ectopic and chaotic sprouting of radial nerve fibers down into the scala tympani and spiraling hundreds of micrometers in the connective tissue encasing the implanted CI (Glueckert et al., 2008; Leake et al., 2011, 2013; Staecker et al., 1996). Ectopic fibers come in

both myelinated and unmyelinated forms, and they clearly show ectopic sprouting (i.e., normally, SGN peripheral axons never appear in the scala tympani, but are limited to the osseous spiral lamina and organ of Corti). Furthermore, even though these animals were given BDNF at one month of life, the structure of the cat's cochlea is mature at this age, and the sprouting fibers were still there when the mice were evaluated as young adults at around six months of age. Importantly, Glueckert et al. (2008) used immunolabeling after a combination of BDNF and FGF treatment to show that both the fibers within the osseous spiral lamina and the ectopic fibers elicited by BDNF treatment were afferent peripheral processes of SGNs, making them relevant to CI stimulation. However, efferent fiber survival was unaffected. Finally, electrophysiological recordings from the inferior colliculus in deafened, BDNF-treated animals have revealed that such sprouting can compromise the CI's optimal function by degrading the normally precise cochleotopic organization of the radial nerve fibers, and thus the selectivity of CI stimulation channels in the auditory midbrain (Leake et al., 2013). Recent developments in CI technology, including current focusing and virtual channel stimulation, rely on very spatially confined SGN activation, which would be harmed by sprouting.

3. Gene therapy for cochlear neurotrophin

Recent breakthroughs in cochlear molecular therapeutics, which have been addressed in numerous earlier papers in this Special Issue, are showing promising results in the development of therapeutic therapeutics for hearing loss by focusing on the correction of genetic abnormalities that cause hair cell loss. Preclinical studies have shown a potentially crucial role for NT treatment in reducing SGN degradation after deafness and enhancing Cis outcomes, as we've already said. Virally-mediated gene therapy has the benefit of needing only a single injection to induce safe and long-term expression of NTs by cells within the target tissue.

3.1. Rodent research

Several investigations in deafened mouse models have found that virally-mediated NT cochlear gene therapy employing a variety of NTs (BDNF, GDNF, NT3, CNTF, and others) reduces SGN degeneration and improves survival following damage. Ad vectors were used in the majority of previous research. Following cochlear administration of vectors pushing expression of NTs, notably BDNF, several investigations in deafened guinea pigs have observed higher SGN survival relative to contralateral after cochlear administration of vectors pushing expression of NTs, notably BDNF (Atkinson et al., 2012, 2014; Chikar et al., 2008; Nakaizumi et al., 2004; Rejali et al., 2007; Shibata et al., 2010; Wise et al., 2010, 2011).

Furthermore, research in additional deaf animal models, such as deaf mutant mice (Fukui et al., 2012) and rats exposed to blasts (Wu et al., 2011), has shown better SGN survival following virally-mediated NT delivery to the cochlea, confirming the cross-species hypothesis. After NT gene therapy, several research groups have observed better survival or signs of resprouting of the radial nerve fibers (the peripheral processes of the SGNs) (Atkinson et al., 2012, 2014; Chen et al., 2018; Fukui et al., 2012; Shibata et al., 2010; Wise et al., 2010). Because the fibers are closer to the CI electrodes, this might help CI function by lowering electrical stimulation thresholds and boosting spatial selectivity and temporal coding. Following cochlear NT gene therapy, certain studies have found indications of functional benefits with an implanted CI (Chikar et al., 2008; Budenz et al., 2015; Pfingst et al., 2017).

Most recent studies have used AAV vectors to drive expression of NT-3 and/or BDNF and have demonstrated excellent success in enhancing both SGN and radial fiber survival (Budenz et al., 2015; Pfingst et al., 2017; Chen et al., 2018). This switch to AAV was most likely motivated by the fact that AAV has been demonstrated to efficiently transport toxins to the inner ear while also being non-ototoxic (Ballana et al., 2008; Konishi et al., 2008; Lustig and Akil, 2012; Gyorgy et al., 2017; Pfingst et al., 2017; Suzuki et al., 2017; Tao et al., 2018). Furthermore, AAV has already been used in clinical trials with no negative consequences (see section 3, below). In deafened, implanted guinea pigs, Pfingst et al. (2017) documented the long-term (although varied) efficiency of AAV-mediated NT-3 gene therapy, as well as showing that psychophysical and electrophysiological techniques may be relevant for monitoring SGN density in the implanted cochlea. Budenz et al. (2015) found that while BDNF was more effective than NT-3 in preventing SGN degradation and improving long-term neural survival following deafness, NT-3 was more successful in triggering radial nerve fiber regrowth. These researchers believe that over-expression of both BDNF and NT-3 in combination may be the most effective way to improve overall neuronal survival.

3.2. Research on cats

The encouraging findings of NT gene therapy in deafened rodents prompted a new study to explore the possibilities for using gene therapy in the considerably bigger feline cochlea, bringing the results closer to the human cochlea (Leake et al., 2019). The animals were deafened as newborns before hearing onset (systemic neomycin injections) to imitate congenital deafness, which was a new component of this investigation. To allow for comparison with earlier studies in which exogenous BDNF was delivered by osmotic pumps at this age (Leake et al., 2011, 2013), and with the rationale that long-term SGN survival and improved CI outcomes are especially important for the pediatric population, gene therapy was administered when the animals were about a month old. AAV2 encoding for BDNF (under control of the CGA promotor) and AAV5-GDNF, both of which have proven effectiveness in previous systems, were compared (CBA promotor). At 3 months after injection, both vectors had minor neurotrophic benefits, with around 6% of the normal SGN population saved compared to the contralateral.

GDNF expression, on the other hand, resulted in undesired fiber sprouting into the scala tympani and did not enhance the number of surviving fibers inside the osseous spiral lamina. In comparison to untreated ears, AAV2-mediated BDNF expression resulted in more than twice the number of surviving radial nerve fibers, with no ectopic or disordered sprouting. Following up on the positive results of AAV2-BDNF, researchers wanted to see if the neurotrophic benefits would last when the post-injection survival time was prolonged to 6 months. Significant neurotrophic benefits were shown in this long-term investigation, with increased SGN neuronal survival maintained throughout the cochlea compared to the contralateral reference. Six months following AAV2-BDNF injections, total mean SGN survival was 53% normal vs. 39% contralateral, indicating that around 14% of the normal SGN population was rescued. When expressed as a percentage increase adjusted to contralateral survival, this translates to a 35 percent increase in SGN survival compared to the control group. It's worth noting that SGN survival in these early-deafened cats was projected to be around 75% of normal at the time of viral injections (1 month of age) (Leake et al., 2011). Despite the fact that AAV2-BDNF evoked a strong neurotrophic effect, the SGNs in the injected ears continued to degenerate. Transfection happens quickly, but only a small number of cells are transduced, and maximal NT expression appears to take significantly longer, according to immunohistochemistry done two weeks after viral injections. The survival of radial nerve fibers in these deafened animals was also measured by counting them in sections cut orthogonal to the radial plane at three different cochlear sites. SGN peripheral fiber survival was consistently greater in the injected ears in all three cochlear regions compared to the contralateral in the 6-month AAV2-BDNF group. After AAV2-BDNF therapy, fiber survival averaged 47 percent of normal, which was twice the value recorded on the opposite side (24 percent of normal).

The findings in a variety of deafened animal models utilizing a variety of viral vectors and NTs delivered to the cochlea imply that NT cochlear gene therapy might be a feasible technique for reducing SGN and radial nerve fiber degeneration after deafness. As a result, a therapy that just requires a single injection has a lot of potential for fostering long-term development in the cochlear neural substrate and, as a result, improving CI results.

3.3 NT gene therapy for cochlear synaptopathy

Animal studies of noise-induced hearing loss have shown that exposures causing only reversible threshold shifts and no hair cell loss can result in permanent loss of SGN synapses on IHCs (cochlear synaptopathy), which can lead to functional deficits and eventually SGN degeneration when followed long-term (Kujawa and Liberman, 2009). Furthermore, multiple investigations have indicated that NT-3 can preserve or even repair IHC synapses, allowing hearing function to be restored after sonic stress (Sly et al., 2016; Suzuki et al., 2016; Wan et al., 2014; Wang et al., 2011). As a result, it's worth noting that AAV-mediated NT-3 overexpression can likewise protect against and heal noise-induced cochlear synaptopathy, according to recent animal research (Chen et al., 2018; Hashimoto et al., 2019).

Furthermore, new research in both noise-exposed and aging human ears has revealed that cochlear synapse degeneration frequently occurs before both hair cell loss and threshold increases (Sereyenko et al., 2013; Kujawa and Liberman, 2015; Liberman, 2015, 2017; Liberman and Kujawa, 2017). Many common perceptual anomalies, including speech-in-noise issues, tinnitus, and hyperacusis, are likely caused by the silencing of afflicted neurons, which drastically changes information processing. As a result, NT gene therapy may one day be effective for prompting SGN peripheral axon resprouting and synaptic regeneration to innervate residual (or regenerated) hair cell populations in situations of "hidden" hearing loss.

4. Non-auditory applications of neurotrophin gene therapy

NTs and members of the neurotrophin family serve crucial roles in the formation, maintenance, and repair of the central nervous system (CNS), much as they do in the auditory system (see Review by Huang and Reichardt, 2001). Several gene therapy approaches have been investigated in animal models and clinical trials of several neurodegenerative diseases, including retinal and optic nerve degeneration, spinal cord injury, Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, over the last three decades (see Review by Blesch et al., 1998; Khalin et al., 2015; Daly et al., 2018; Hardcastle et al., 2018; Hodgetts and Harvey, 2017; Mestre and Sampaio, 2017). Although significant progress has been made, and mounting evidence from animal studies supports the efficacy of neurotrophin gene therapy in preventing neuronal degeneration and promoting neural repair, a number of technical challenges must be overcome before these applications can be successfully applied to human patients. This section focuses on the efficacy of various gene therapy applications as well as the current problems they face. The following discussion outlines our current understanding of how to improve delivery protocols to improve the effectiveness and specificity of NT gene therapy in various neurodegenerative conditions, as well as the implications for possible use in auditory nerve degeneration and hearing loss.

4.1. Neurodegenerative diseases that aren't Alzheimer's

Gene therapy (such as intravitreal gene transfer) has been a popular treatment option for hereditary optic neuropathies and other retinal illnesses due to the retinal ganglion cells' anatomical accessibility (Thanos and Emerich, 2005; Yu-Wai-Man et al., 2014). Although the first results are promising, these gene therapy techniques are still in the early stages of research, and further proof of their efficacy, specificity, and safety is needed before they are applied to human patients. NGF, BDNF, and NT3 are members of the NGF family of NTs, which play important roles in retinal ganglion cell survival. For example, retinal ganglion cells produce BDNF locally (Herzog and von Bartheld, 1998). In various animal models of retinal degeneration, GDNF, a member of the transforming growth factor superfamily, protects the retina (Thanos and Emerich, 2005).

Previous research has suggested that NT deficiency and dysfunction have a role in the etiology of glaucoma (Bringmann et al., 2006; Johnson et al., 2011). In a rat model of optic nerve transection, AV vectors were used to increase Müller glial expression of BDNF (Di Polo et al., 1998). AAV-mediated BDNF transfer to Müller cells protected photoreceptors from light-induced retinal degeneration, according to Gauthier et al. (2005). AAV-GDNF reduced photoreceptor loss for at least 45 days in an animal model of human retinitis pigmentosa (S334ter-4 rhodopsin transgenic rat) using AAV-mediated gene delivery (McGee Sanftner et al., 2001). These findings show that increasing endogenous retinal synthesis of specific NTs via viral vectors might reduce or prevent retinal and optic nerve degeneration.

BDNF is the most studied NT protein in experimental spinal cord injury (SCI), and it is involved in axonal sprouting, neuroprotection, myelination, adaptive synaptic plasticity, synaptic transmission, and antioxidative actions (Kovalchuk et al., 2004; Weishaupt et al., 2012). In a rat model of total spinal cord transection treated with local BDNF overexpression induced by AAV1/2 vectors under control of the neuron-specific human SYN 1 promoter, Ziemlinska et al. (2014) showed a considerable increase in treadmill locomotor capacities. Within 30 minutes following spinal cord transsection, AAV-BDNF intraspinal injections were given, and locomotor function improvement was shown as early as two weeks following therapy and sustained for at least seven weeks. In the AAV-BDNF-treated rats, there was an increase in excitatory neurotransmission-related molecules. Around the damaged region, however, an altered balance of excitatory and inhibitory neuronal activity was found. These modifications might have had a role in the motoneuron hyperexcitability that was common following injury. A retrograde adenovirus (Ad-mediated) BDNF gene transfection resulted in decreased cell death in neurons and oligodendrocytes in a chronic SCI model (twy/twy mice) (Uchida et al., 2012). This neuroprotective effect was observed four weeks after Ad-BDNF administration, but the treated mice were not functionally evaluated. In rat models of spinal cord injury, two previous investigations found that virus-mediated BDNF gene transfection decreased neural cell death and improved axonal regeneration and locomotor functional recovery for at least 6 weeks after injections (Koda et al., 2004; Nakajima et al., 2010). Although AAV-mediated BDNF + GDNF transfection improved motor neuron survival, it did not result in functional recovery following ventral root avulsion (Blits et al., 2003). Martinez-Gálvez et al. (2016) used a cervical spinal cord injury model to show that delivering AAV7-mediated gene transduction for TrkB, a high-affinity receptor for BDNF, improved respiratory function. Research has looked at the efficacy of NT gene therapy employing various members of the NT family, combinations of various NTs, or coupled NT overexpression with cell-based treatment (e.g., stem cell or Schwann cell implants) (see review by Blesch et al., 1998; Hendriks et al., 2004; Harvey et al., 2015; Hodgetts and Harvey, 2017). The injection of an AAV-BDNF and AAV-NT-3 combination into the gray matter of the spinal cord, caudal to a Schwann cell graft implanted in damaged rats, improved locomotor performance, but no evidence of axon regrowth from the Schwann cell implant was seen (Blits et al., 2003). It's worth noting that in all of the experiments described above, virus-mediated gene therapy was delivered immediately or shortly after damage (e.g., within 3 days).

In neuropathological illnesses such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and schizophrenia, dysregulation of NTs such as BDNF and NGF is a crucial component (Phillips et al., 1990; Sampaio et al., 2017; Simmons, 2017). Alzheimer's disease is a neurological illness that progresses over time and is the leading cause of dementia in older people (see review by Loera-Valencia et al., 2019). Reduced NT expression and deregulation of their relevant signaling pathways have been linked to Alzheimer's disease and Parkinson's disease, according to studies (Alves et al., 2016; Ventriglia et al., 2013). Several animal studies (Nagahara et al., 2009, 2013; Alves et al., 2016; Jiao et al., 2016) as well as clinical trials have revealed varying levels of effectiveness in NT gene therapy employing a viral-based delivery strategy (Rafii et al., 2014; Tuszynski et al., 2015; Malkki, 2015). The injection of lentivirus-mediated BDNF into the cortex of APP amyloid-transgenic mice, an animal model of Alzheimer's disease, increased synaptic protein production, reversed synapse degradation, and restored learning and memory performance (Nagahara et al., 2009). A comparable lentivirus-mediated BDNF therapy was given to both elderly rats and primates in this investigation. 2–4 weeks following therapy, these rats showed improved cognitive performance as well as decreased neuronal atrophy. However, the positive neuroprotective impact was not reliant on the presence of amyloid plaques. Jiao et al. (2016) used BDNF gene therapy in P301L mice, an Alzheimer's disease animal model characterized by age-related tau pathology and memory loss. Before severe tau pathology and cognitive impairment, the mice were given intraventricular injections of AAV8-BDNF at 3 months of age. 9 months following therapy, neuronal structures were restored and cognitive function improved, but there were no improvements in the tau pathogenic status.

Another key NT is NGF, which is required to prevent the loss of basal forebrain cholinergic neurons, which are commonly lost early in Alzheimer's disease. Several Phase I clinical trials have revealed that virus-mediated NGF treatment might prevent or minimize cholinergic neuron degeneration in Alzheimer's disease patients. In one study, AAV2-NGF was injected bilaterally into the basal forebrain areas of ten Alzheimer's disease patients (Rafii et al., 2014). All of the patients' brains showed a trophic response to NGF transduction, as well as a slower pace of cognitive deterioration. The bioactivity of AAV2-mediated NGF expression was discovered in brain autopsy tissues in this work; the longest post-treatment evaluation time was roughly 24 months, indicating that this technique may be practical and capable of creating reasonably long-term and physiologically active NT expression. NGF was previously given by autologous fibroblasts transfected with NGF-leukemia viruses and transplanted into the basal forebrain area containing cholinergic neurons (Tuszynski et al., 2005). Over the course of a two-year monitoring period, this ex vivo investigation found structural and functional improvements. The same group's second phase I investigation found that deteriorated neurons responded to NGF gene therapy in all patients (Tuszynski et al., 2015). The participants in this research were followed for periods ranging from 11 months to ten years. These findings imply that ex vivo or in vivo administration of the virus-mediated neurotrophin gene might be used to treat Alzheimer's disease and other neurodegenerative illnesses.

4.2. In non-auditory systems, lessons learnt from NT gene therapy research

A rising body of research suggests a relationship between age-related deafness, blindness, and dementia (see reviews by Mancino et al., 2018; Chern and Golub, 2019), pointing to shared processes of neurodegeneration in the peripheral auditory nerve, retinal and optic nerve, and the brain. It's also plausible that the loss of sensory information and social contact has a negative impact on neurocognitive function, hastening cognitive decline. Recent research into cochlear implantation in older people has found improvements in attention and working memory, such as with the operation span task, as evidence for this concept (Volter et al., 2018). A better understanding of the challenges and issues identified in studies of NT gene therapy in retinal and optical nerve degeneration, spinal cord injury, Alzheimer's disease, and other neurodegenerative disorders has significant implications for the design and refinement of investigations into these applications in the auditory system and hearing loss. Three important challenges are explored here in order to better understand how to improve the efficacy of NT gene therapy techniques. First, the efficacy of NT gene therapy is very time-dependent, with the better outcome occurring earlier in the illness stage when treatment is initiated. The therapies were administered either immediately or shortly after damage in most of these animal experiments, as described above under CNS trauma such as spinal cord damage. Similarly, late-stage patients with Alzheimer's disease and other neurodegenerative disorders had little response to neurotrophic gene therapy (Bartus and Johnson, 2017b). A better understanding of the dynamic changes in endogenous NF expression features in different populations of neural cells and conditions of inflammation after CNS injury or at different stages of neurodegenerative disease would be beneficial. Second, determining the appropriate places to inject gene therapy reagents is crucial. Because the method may deliver regulated, long-term physiologically active NTs in the targeted areas or cells, virus-mediated gene therapy has emerged as a viable therapeutic strategy for SCI, Alzheimer's disease, and other neurodegenerative diseases. For many of these uses, however, creating an effective and safe administration method remains a difficulty. For example, the ex vivo delivery strategy for NGF gene transduction in the cholinergic neurons of the basal forebrain area was developed in the phase I clinical trial of Alzheimer's disease stated above (Tuszynski et al., 2005). Finally, more research is needed to discover the optimum method for administering the medication and if a certain quantity or amount of virus is sufficient (Harvey et al., 2015; Bartus and Johnson, 2017a, 2017b). Potential consequences of exogenous neurotrophin gene expression on the function of host neural cells, such as neurotransmitter dysregulation or impairment of brain plasticity, must be carefully considered. For example, in some situations of spinal cord damage, overdosing on neurotrophic factors may result in adverse effects such as increased sensitivity to pain or seizures (Cunha et al., 2009; Weishaupt et al., 2012; Hodgetts and Harvey, 2017). Negative feedback of the BDNF/TrkB signaling pathway and ‘trapping' of regenerated axons results from continued high levels of BDNF expression (Eaton et al., 2002; Blits, 2003).

5. Clinical application future aims and obstacles

Preclinical cochlear gene therapy research has focused on the preservation of SGNs in order to either preserve/restore hearing or improve the performance of cochlear implants. As previously mentioned, multiple studies have shown that Ad or AAV-mediated delivery of NTs (BDNF, GDNF, and NT-3) can help to prevent cochlear SGN degeneration following deafness. Cochlear gene therapy, unlike traditional pharmacological therapies, is a complicated biological treatment whose success is dependent on a variety of circumstances. These include, but are not limited to: 1) viral vector design optimization (safety, toxicity, and target specificity) and high quality vector production (efficacy at the lowest possible dose; ability to replicate long-lasting and stable levels of expression); 2) viral delivery site and method; and 3) intervention at an appropriate stage of the hearing disorder.

5.1. Choosing the best viral vector (s)

Previous gene therapy research has documented a number of modified replication-deficient viral vectors, including the Ad and AAV vectors, which have emerged as the most extensively employed tools for virally-mediated transport of NTs to the cochlea.

Adenovirus (Adenovirus) (Adenovirus) (Adenovirus

In the last two decades, ad has become a popular candidate for gene therapy (Lee et al., 2017).As a result, it's no surprise that it's one of the two main viral vectors utilized in cochlear gene therapy (Praetorius et al., 2009; Staecker et al., 2014). Ads have a relatively large cloning capacity of more than 10 kb and have tropism for a variety of cochlear cell types, which are two benefits for gene delivery. Because many illnesses are caused by mutations in genes with coding sequences that exceed the AAV capacity, the cloning capacity is critical. As a result, ad vectors have a significant advantage over AAV in terms of cloning capacity. The length of transgenic expression is generally a few weeks to months, which is beneficial for applications that need a limited time for expression. This is also one of its major drawbacks for NT gene therapy or hereditary causes of hearing loss, where long-term gene expression is critical. Another drawback of the ad is its proclivity for eliciting an immunological response. Although newer generations of ads have been developed to lessen this risk, if repeated administration is necessary, immune-related adverse effects may be exacerbated. Despite their great cloning capability, the more intricate structure of Ad and the higher potential for eliciting undesired immune responses may restrict their use in the ear.

5.1.2. Adeno-associated virus

AAV as a gene therapy vector has been used in several studies to partially or completely restore hearing loss in mouse models of hereditary deafness (Akil et al., 2012; Askew et al., 2015; Emptoz et al., 2017; Geng et al., 2017; Isgrig et al., 2017; Pan et al., 2017; Akil et al., 2019a, b; see other papers in this Special Issue). AAV vectors have the capacity to effectively transduce cells that have completed mitosis (Colella et al., 2018). They also offer superior safety profiles (low immunogenicity), which gives them a leg up over ads. Furthermore, it has been established that AAV is not ototoxic (Ballana et al., 2008; Konishi et al., 2008; Lustig and Akil, 2012; Gyorgy et al., 2017; Pfingst et al., 2017; Suzuki et al., 2017; Tao et al., 2018). Importantly, AAV vectors have been shown to be effective for gene delivery to the eye and other organs in proof-of-concept investigations and clinical trials (Simonelli et al., 2010; Flotte et al., 2011; Nathwani et al., 2011; Bowles et al., 2012; Le Meur et al., 2018). Furthermore, non-replicating recombinant AAV vectors may efficiently deliver transgenes to a variety of cochlear cell types, including non-dividing neurons and hair cells. The virus does not integrate into the host genome; instead, it stays episomal, resulting in stable, long-term transgenic expression (Xia et al., 2012). Because long-term expression is vital for many human applications, AAV vectors' long-term expression provides a significant advantage over Ad vectors. Because NT expression is likely to be necessary in the long run, AAV vectors may be the best alternative for delivering NTs to the inner ear. Finally, the cochlea is a good candidate for gene transfer because it is separated from the rest of the body, reducing viral propagation and immune system exposure.

5.1.3. Serotypes and promoters

Tissue-specific promoters can be used to achieve specificity in gene delivery. Although using a cochlear cell-specific promotor to guide transgene expression may reduce undesirable off-target effects, it is uncertain if the promotor truly improves cochlear cell transduction efficiency. In other tissues, such as the heart (Ai et al., 2008; Merentie et al., 2016), toxicity and inflammation have been observed with widely active promoters (CMV, CBA, etc.) but not with cell-type–specific promoters (Klein et al., 2006; Watakabe et al., 2015). One possible explanation for this toxicity is because widely active promoters generate greater transgenic expression than cell-type–specific promoters. The use of cell-specific promoters can limit transgenic expression in non-target cells and improve gene delivery specificity to the cell type of interest. There are a variety of potential cochlear cell-type-specific promoter options to choose from. Myosin VIIA promoter, elongation factor 1 promoter, neuron-specific enolase promoter, and glial fibrillary acidic protein promoter are examples of such promoters. These promoters have been cloned and studied in detail. The myosin VIIA promoter, which is expressed strongly and selectively in the hair cells of the cochlea and vestibule, was identified by Boeda et al. (2001).

Following cochlear injection in adult rats and mice, Lui et al. (2007) found that the myosin VIIA promoter generated selective expression of eGFP inside hair cells. The neuron-specific enolase promoter and the elongation factor 1 promoter both induced selective eGFP expression inside SGN and spiral ligament cells, according to these same researchers (Lui et al., 2007). Rio et al. (2002) had previously discovered glial fibrillary acid protein promoter selectivity in all cochlear supporting cells shortly after birth.

Transfection specificity can also be achieved by retargeting AAV to distinct cellular receptors or utilizing various AAV serotypes with various binding sites (Nam et al., 2011). The vitality of the cochlear cells targeted for viral transfection is expected to determine the efficacy of NT gene therapy. When the organ of Corti (OC) is chosen as the target (Wise et al., 2010), continuing degradation due to hearing disease may restrict the ability of NT gene therapy to offer the neurotrophic support required to protect SGNs. Even after significant OC degradation, viral transfection of cells inside the scale medium was still achievable (Wise et al., 2011). Supporting cells (e.g., pillar and Deiters' cells), cells inside the stria vascularis and spiral ligament of the cochlear lateral wall, endosteal cells covering the scala compartments, and interdental cells inside the spiral limbus are all examples of these cells (Wise et al., 2011). The AAV serotype, viral load, and promoter combinations that successfully transduce various auditory cell types are largely understood. Therefore, optimizing transduction efficiency is critical to enhancing the therapeutic impact of NT gene therapy. Various AAV serotypes, including AAV2 (Budenz et al., 2015; Pfingst et al., 2017; Leake et al., 2019), AAV8 (Chen et al., 2018), and AAV5 (Chen et al., 2019), have been employed for neurotrophin administration in animal investigations (Leake et al., 2019). Despite the fact that all of these studies showed an increase in SGN survival after deafness, there is no direct comparison of the efficacy of the various AAV serotypes used for NT gene therapy due to differences in other variables such as animal models, delivery sites and methods, virus concentration and dose, and so on. Kilpatrick et al. (2011) studied the transduction effectiveness and cellular specificity of multiple AAV vectors (serotypes 1, 2, 5, 6, and 8) in normal and drug-deafened ears in a single research. This study found that all five AAV serotypes effectively transduced the above-mentioned common cochlear cell types, implying that any of the AAV serotypes may be utilized for effective NT SGN gene therapy. The recombinant AAV2 serotype, on the other hand, appears to be the best option for two reasons: 1) It effectively transduces the cochlear cells that are being targeted. 2) It is the most often utilized viral vector in clinical trials for other organs (e.g., ocular gene therapy), and it is now being utilized to treat Leber's congenital amaurosis (Cideciyan et al., 2013; Bainbridge et al., 2015; Russell et al., 2017) and choroideremia (Cideciyan et al., 2017). (MacLaren et al. 2014; Edwards et al. 2016).

To date, research has shown that for each viral design, sensitive tests must be developed that are particular to the organ and cell types being targeted. Such tests will allow the development of vectors that may be safely used to deliver optimal dosages of vectors, potentially improving both safety and effectiveness (Xiong et al., 2019). If safer vectors can be developed, a larger number of cochlear cells could be transduced, resulting in increased effectiveness and fewer safety issues.

5.2. Determining the optimal concentration/dosage; clinical consequences

While inner ear gene therapy may prove to be a beneficial therapeutic technique in the future, safety concerns about viral gene delivery must be carefully examined in relation to the procedure's predicted advantages. It will be important to discover a viral titer that would offer the intended benefit while provoking minimum or no harm in order to optimize virus-mediated gene therapy for clinical use. The viral dosage and the promoter are the two parameters that influence a viral vector's transduction effectiveness, and they also have the strongest link to toxicity. Other factors are likely to have a role in toxicity as well (e.g., stocks with a high degree of endotoxin, or non-viral protein contamination). This emphasizes the need for tailoring the viral load and promoter design in the development of cochlear-targeted gene therapy in order to maximize the therapeutic impact.

5.2.1. Dose of vector

Current cochlear local delivery methods can result in just a small fraction of target cells being transfected since they are close to the injection site. A more thorough infection would almost certainly increase the intended effect (S), but it would necessitate a higher viral load, which might cause toxicity. In animal investigations, toxicity associated with greater dosages has been shown in the eyes and other organs (Mingozzi and High, 2013; Hinderer et al., 2018; Vandenberghe et al., 2011; Ramachandran et al., 2017; Khabou et al., 2018). According to Akil et al., 2019a, the overexpression of hGDNF induced by AAV5-hGDNF in newborn mice resulted in severe neurological symptoms and hearing loss due to Purkinje cell loss and cochlear nucleus pathology.Extremely high levels of transgenic protein expression should thus be avoided, especially for proteins with potential neurological roles (Akil et al., 2019a). This can be accomplished by lowering the amount of virus injected into the ear to reduce toxicity while still ensuring that the protein of interest is expressed at a high level in the targeted cells.

5.3. Scala tympani vs. Scala media as a route to administration.

Various gene delivery pathways have been successfully applied to sensory hair cells, spiral ganglion neurons, and cells in the stria vascularis in a variety of animal experiments (see Lustig and Akil, 2012; Géléoc and Holt, 2009; Chien et al., 2015; Ma et al., 2019). The surgical delivery to the inner ear space, which must limit harm to the inner ear while maximizing viral transduction of the target cells across the cochlea while retaining hearing function, is perhaps the most predictable of all the factors. The dosage delivered to the target cells may be reduced if the vector is reabsorbed outside of the cochlea. In addition, the injected vector particles may trigger an immune response against the viral capsids, reducing the quantity of effective vector particles in the cochlear region.

For effective targeting of cochlear cells, a safe and repeatable delivery of gene therapy vector into the inner ear is required. The comparison here is between two major delivery routes: 1) into the perilymph of the scala tympani, and 2) into the endolymph of the scala media. The most common approaches to cochlear gene therapy have been scala tympani operations, which can be done through the round window membrane, oval window, or direct cochleostomy via the bone otic capsule. Among them, the route through the round window membrane has been recognized as the best strategy for conserving residual hearing, and multiple investigations have shown that NT gene therapy using this technique is successful. However, as compared to the scala media technique, the scala tympani technique demonstrated reduced transduction effectiveness in cochlear cells. A cochleostomy via the cochlear lateral wall or a direct injection through the basilar membrane are used to reach the scala media pathway (Shibata et al., 2009; Wise et al., 2010: Kilpatrick et al., 2011; Chang et al., 2015). Due to the intricacy of the organ of Corti and the significance of the endolymphatic barrier and ion homeostasis for optimal hearing function, surgical operations for this pathway are more likely to cause hair cell injury and hearing loss. Kilpatrick et al. (2011) described an effective AAV inoculation method in mice's ears using the scala medium with little injection stress. The quantity (350 nl) and pace of injection into the scala media via the cochlear lateral wall were accurately controlled in this work using a microinjection device (WPI) capable of delivering quantities in the nanoliter (nl) to microliter (l) range. In adult mice deafened with kanamycin and furosemide, this method resulted in high AAV8 transduction efficiency in the auditory nerve. Finally, the best injection site will be determined by the precise cells that the gene therapy is targeting. The scala tympani, for example, is likely to be a superior choice if the SGNs are the target cells since it is right near to Rosenthal's canal, whereas the scala medium is considerably further away from the ganglion. Furthermore, strong junctional complexes across all cells isolate the scala media from the rest of the cochlear structures, restricting this specific fluid region.

5.4. Administration timing; consideration of the host cochlear milieu, glial cell activation, and post-deafness inflammatory reactions

The time of the therapeutic agent's delivery is a critical component in neurotrophin gene therapy's success. Gene therapy research, including Alzheimer's disease and CNS damage such as spinal cord damage, as discussed above, implies that the earlier the treatment (e.g., gene therapy administered soon after damage), the better the results (Harvey et al., 2015; Bartus and Johnson, 2017a, 2017b). Early treatment is thought to reduce axonal retraction, preserve myelin, and modulate the phenotype and activation of microglia/macrophages recruited from the circulation. Loss of the auditory nerve occurs in the peripheral auditory nervous system as a consequence of either primary or secondary degeneration after hair cell loss as a consequence of cochlear insults (Spoendlin, 1984; Leake and Hradek, 1988; Kujawa and Liberman, 2009; Lang, 2015a, b; Liberman, 2015).

Following cochlear insult caused by noise exposure and the administration of ototoxic medications, many pathological changes emerge in non-neuronal cells of the damaged auditory nerve. Demyelination, disruption of the Ranvier node, and activation of glial cells, as well as enhanced macrophage recruitment and activation, are among the pathogenic alterations (or other immune cells). Importantly, as observed in multiple animal investigations, all of these pathogenic changes occur in a time-dependent sequence (Lang et al., 2011, 2015; Tagoe et al., 2014; Panganiban et al., 2018; Kohrman et al., 2019). Previous research has revealed that in order for the NT treatment to be successful, it must be used in the early stages of illness, when there are still enough healthy neurons to react to treatment (Harvey et al., 2015; Quintino et al., 2019). However, the onset of SGN degenerative changes differs substantially between animal models (Wise et al., 2011; Leake et al., 2019). In applications of NT gene therapy, careful timing of administration should be included in the experimental design, based on consideration of the cochlear pathophysiological circumstances following deafness, in particular, the pathologies of these non-neuronal cells.

5.5. Administration site: endogenous cochlear NT expression tonotopic gradients

Both physically and functionally, the neurotrophins BDNF and NT3 play critical roles in the formation and early maintenance of the auditory nerve's tonotopic organization (Pirvola et al., 1992; Davis, 2003; Flores-Otero et al., 2007; Fritzsch et al., 2015). The Bdnf gene knockout produces a considerable loss of basal turn spiral ganglion neurons, whereas the NT-3 gene knockout produces a considerable loss of auditory nerve innervation to hair cells in the apical turn (Fritzsch et al., 1997). Furthermore, in both the postnatal and adult auditory nerves, BDNF has a greater expression in the basal area, but NT-3 appears to have a larger concentration in the apex (Farias et al., 2001; Sugawara et al., 2007). Adamson et al. (2002) used a unique in vitro setup to show that BDNF and NT3 had opposing impacts on SGN firing patterns. In particular, BDNF increased the activity of the SGNs in the apex, but had no effect on the neurons in the basal turn. In contrast, when neurons in the apex and base were exposed to NT-3, their firing patterns resembled those of the apical control. It is critical to evaluate the right location and cells in the cochlea that the gene therapy would target, similar to the present issues we outlined above in the research of spinal cord damage and Alzheimer's disease. When developing innovative therapeutic uses of NT gene therapy, it may be critical to consider how to minimize or prevent disrupting the tonotopic firing features of the surviving SGNs. The gene therapy must be tailored to maintain/restore the normal intrinsic firing properties of the SGN in order to achieve the long-term objective of restoring hearing through hair cell regeneration or attaching surviving hair cells to the auditory nerve. On the other hand, inherent firing features of SGNs may be overpowered by the more crude direct electrical stimulation supplied by a CI, and hence may not be as significant in the case of prospective use of NT gene therapy to sustain increased survival of SGN for application of a CI.

6. Conclusions

NT cochlear gene therapy might possibly provide a single treatment that might dramatically improve neuronal survival and results in CI patients if the multiple problems listed above can be appropriately addressed and safety concerns allayed by additional study in animal models. This is especially critical for pediatric CI patients, who must rely on electrical hearing for the rest of their lives and whose results are very diverse (Svirsky et al., 2000; Ortmann et al., 2017; Zhao et al., 2019).

Furthermore, in the future, NT gene therapy may have the potential to help individuals with noise-induced hearing loss or neural presbyacusis (e.g., age-related cochlear synaptopathy), in whom primary neuronal loss is a major cause of hearing loss. Animal investigations of noise-induced hearing loss have demonstrated that even exposures that cause only reversible threshold changes and no hair cell loss can result in permanent loss of SGN synapses on hair cells, resulting in functional deficiencies and eventually SGN degeneration (Kujawa and Liberman, 2009). Degeneration of cochlear synapses often precedes both hair cell loss and threshold increases in human ears, according to current studies (Sereyenko et al., 2013; Kujawa and Liberman, 2015; Liberman, 2015, 2017). Cochlear synaptopathy has been described as "hidden" hearing loss in ears with intact hair cell populations and normal audiograms (Schaette and McAlpine, 2011). Many common perceptual anomalies, including speech-in-noise issues, tinnitus, and hyperacusis, are likely caused by the silencing of afflicted neurons, which changes information processing dramatically. Thus, NT gene therapy may be effective in the future in prompting SGN peripheral axon resprouting and synaptic regeneration to innervate residual (or even regenerated) hair cell populations. We have shown strong evidence that BDNF gene therapy can increase SGN survival and stimulate maintenance or resprouting of peripheral axons in this study. In adult animals exposed to acoustic damage, NT-3 has been found to induce synaptic regeneration of these fibers, reconnecting them to the hair cells and their ribbon synapses, as well as to restore hearing function (Sly et al., 2016; Suzuki et al., 2016; Wan et al., 2014; Wang et al., 2011; Hashimimoto et al., 2019). As previously proposed by Budenz et al. (2015), combining BDNF and NT-3 gene therapy may be the most effective way to maintain/restore a more normal cochlear neuronal substrate.

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