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REVIEW **Open Access**

Neuroprotective role of insulin-like growth factor 1 in auditory and other nervous systems

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Summary. Insulin-like growth factor 1 (IGF1) exerts an influence on almost every organ system in the body and plays an important role in growth, development, and metabolism. In the nervous system, IGF1 acts by promoting the development and growth of neurons and glial cells, differentiation of Schwann cells and their migration to axons, neurite outgrowth, and neuronal survival. The lack of IGF1 is associated with several pathological conditions, including severe prenatal growth retardation, postnatal growth failure, microcephaly, mental retardation, and bilateral sensorineural hearing loss. In addition to its physiological effects, based on the findings of in vivo and in vitro experiments and clinical trials, IGF1 is considered to play a potential role in the treatment of various types of neuronal damage. In this review, we discuss the potential use of IGF1 as a therapeutic molecule in the nervous system: (1) auditory system, including hair cells, cochlear ribbon synapses, auditory nerve, and central nervous systems, and (2) other peripheral nervous systems, especially the olfactory system and facial nerve. The role of IGF1 in the progression of age-related sensory deficits, especially hearing loss and olfactory dysfunction, is also discussed. Recent studies on IGF1 demonstrated that exogenous IGF1 can be applied in many fields, thus supporting the continued evaluation of IGF1 as a potential therapeutic molecule. Additional scientific investigations should be conducted to further supplement recent findings.

Key words: Insulin-like growth factor 1, Sensorineural hearing loss, Olfactory dysfunction, Facial nerve damage

Introduction

Early studies have provided evidence that insulin-like growth factor 1 (IGF1) exerts an influence on almost every organ system in the body, playing an important role in growth, development, and metabolism (Pages et al., 1993; Shepherd et al. 1998; Holmstrom et al., 1999; Laviola et al., 2007; Dyer et al., 2016; Nieto-Estévez et al., 2016; Dixit et al., 2021). IGF1 is a hormone that is structurally similar to insulin. IGF1 was first named somatomedin-C but was renamed because of the high degree of sequence identity between IGF1 and insulin. The insulin-like activity of IGF1 is markedly lower than that of insulin, but cell proliferation is 50-100 times higher in IGF1-treated cells than in insulin-treated cells (Rinderknecht and Humbel, 1976). In mammals, IGF1 is mainly synthesized in the liver, and most circulating IGF1 forms a complex with its binding protein, IGFBP1-6 (Bach, 2018).

At the cell surface, IGF1 binds to the high-affinity IGF1 receptor (IGF1R), activating two main downstream signaling pathways (Murillo-Cuesta et al., 2011; Hayashi et al., 2013; Yamahara et al., 2015; Rodriguez-de la Rosa et al., 2017). One pathway is the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, in which phosphorylated PI3K activates Akt, whereas the other is composed of Ras, Raf, and mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) kinase (MEK), which activates ERK and is termed the MEK/ERK pathway. Both pathways are important for cell survival, differentiation, proliferation, and maintenance of normal physiological conditions in various organs (Holmstrom et al., 1999; Laviola et al., 2007; Dyer et al., 2016; Osher and Macaulay, 2019; Gao

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Abbreviations. AN, acoustic nerve; ARHL, age-related hearing loss; CI, Cochlear implants; CtBP2, C-Terminal Binding Protein 2; EAS, electric-acoustic stimulation; FC, fusiform cell; GluA2, AMPA receptor 2; HC, hair cell; IGF1, Insulin-like growth factor 1; IGFBP, Insulin-like growth factor binding protein; IGF1R, Insulin-like growth factor 1 receptor; MAPK/ERK, mitogen-activated protein kinases/extracellular signal-regulated kinases; OE, olfactory epithelium; OMP, olfactory marker protein; ORN, olfactory receptor neuron; PI3K, phosphatidylinositol 3-kinase; SGN, spiral ganglion neuron; SNHL, sensorineural hearing loss.

et al., 2020).

In humans, patients with homozygous IGF1 mutations present several types of abnormalities, including severe prenatal growth retardation, postnatal growth failure, microcephaly, mental retardation, and bilateral sensorineural hearing loss (ORPHA73272, OMIM 608747) (Woods et al., 1996, 1997; Bonapace et al., 2003; Walenkamp et al., 2005). The survival and proliferative effects of IGF1 on various organs suggest the possible use of IGF1 for disease treatment. Here, we review the literature to illustrate the potential use of IGF1 as a therapeutic molecule for the nervous system, including the auditory system and other peripheral nerves.

Auditory system

Physiological role of IGF1 in the auditory system

Sound vibration travels from the external and middle ear to the organ of Corti. The sensory epithelium of the organ of Corti contains highly differentiated cells and inner and outer hair cells (HCs), which transform mechanical sounds into neural signals that are conveyed to the brain. The organ of Corti is connected to the brain by two types of neurons in the spiral ganglion neurons (SGNs); type I and type II neurons innervate inner and outer HCs, respectively. The SGN axons form the acoustic nerve (AN) and connect the peripheral spiral ganglia with the cochlear nuclei in the brainstem. Sound information progresses in a complex multisynaptic, parallel, and ascendant pathway from the cochlea to the brainstem nuclei (cochlear nuclei and superior olive), midbrain (inferior colliculus), thalamus, and auditory cortex, preserving the tonotopic organization (Fig. 1A-D) (Tsukano et al., 2017).

Hearing loss has a huge impact on affected individuals and society. Current data suggest that approximately 5% of the world's population (that is 466 million people) suffer from hearing loss (Schmucker et al., 2019). Hearing loss can be subdivided into two types: conductive and sensorineural hearing loss (SNHL). Although conductive hearing loss can be cured by surgical treatments, hearing abilities in patients with SNHL, in general, are never recovered once they are lost. SNHL is characterized by the degeneration of key structures in the sensory pathway, such as HCs, ANs, and their synaptic connections to HCs, the cochlear ribbon synapse, and the ascending auditory pathways from the cochlear nuclei to the auditory cortex. Various strategies to protect or regenerate these structures have been the subject of intensive research.

IGF1 plays an important role in the development and maintenance of the auditory system (Murillo-Cuesta et al., 2011; Okano et al., 2011). Mice deficient in *Igf1* have severe hearing loss (Camarero et al., 2001; Cediel et al., 2006) and exhibit reduced cochlea size, an immature tectorial membrane, and significantly decreased cochlear ganglion numbers and sizes (Camarero et al., 2001). IGF1 also plays a role in brain neurodevelopment, and in *Igf1* null mutant mice, brain weight is reduced by 29-38% (Ye et al., 2002).

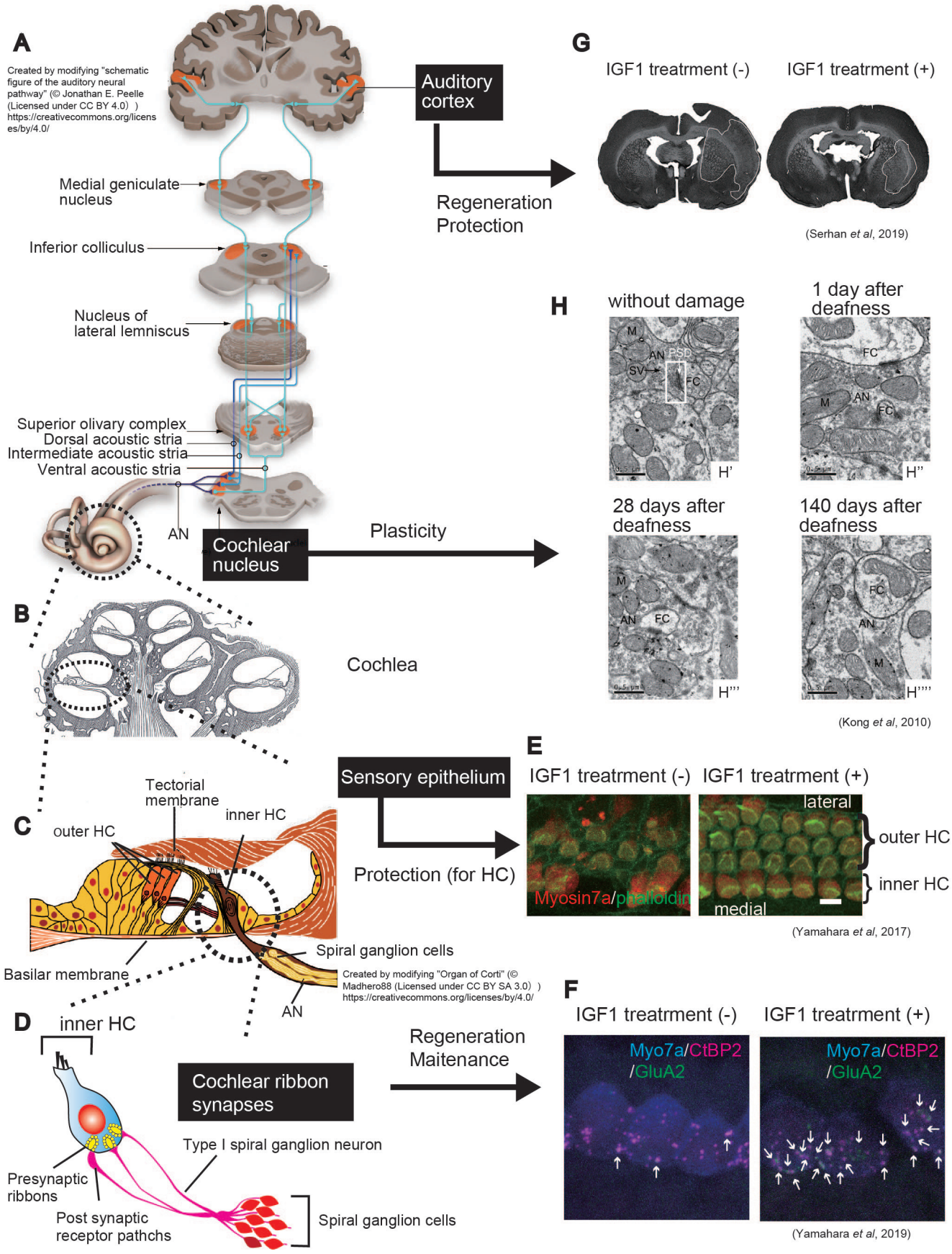
Effects of IGF1 on the damaged auditory pathway

Hair cells

HCs have long been thought to be the most vulnerable elements to various ototoxic events. SNHL is caused by functional impairment or loss of HCs in many cases. HC damage may result from a variety of factors, including genetic disorders, infectious diseases, overexposure to intense sounds, and certain drugs. After birth, the mammalian cochlear HCs cannot regenerate if injured because HCs lose their ability to proliferate during embryogenesis (Ruben, 1967; Laine et al., 2010). Therefore, the maintenance of HC numbers after a cochlear injury is important for treating SNHL.

To assess the effects of IGF1 on inner ear damage, IGF1 was administered to animals with HCs damaged by several types of insults, such as noise, ischemia, or surgical trauma (Iwai et al., 2006; Lee et al., 2007; Fujiwara et al., 2008; Yamahara et al., 2018). As the first step toward studying the effects of IGF1 on HC damage, prophylactic treatment with IGF1 to protect HCs against noise exposure was investigated (Iwai et al., 2006). IGF1 was administered to adult rats before noise exposure, which resulted in significant attenuation of hearing

Fig. 1. Auditory pathway and IGF1 targets. IGF1 targets are shown as white characters on a black background. **A-D.** Schematic of the auditory pathway **(A)** (Created by modifying "schematic figure of the auditory neural pathway" (© Jonathan E. Peelle (Licensed under CC BY 4.0)) https://creativecommons.org/licenses/by/4.0/), Cochlea **(B)** (Gray and Carter, 2019), Sensory epithelium **(C)** (Created by modifying "Organ of Corti" (© Madhero88 (Licensed under CC BY SA 3.0)) https://creativecommons.org/licenses/by/4.0/), and inner HC and Cochlear ribbons synapses **(D)**. **E.** IGF1 protects HCs against neomycin (Yamahara et al., 2017). IGF1 treatment maintained the HC number against neomycin damage **(E)**. Scale bar represents 10 μm. **F.** IGF1 affects the maintenance and regeneration of cochlear synaptic ribbons (Yamahara et al., 2019). C-terminal binding protein 2 (CtBP2) and AMPA receptor 2 (GluA2) were stained to label the presynaptic ribbons and postsynaptic receptor patches, respectively. CtBP2/GluA2 double-positive puncta in each inner HC were counted as live synapses. Arrows indicate puncta co-stained with CtBP2 and GluA2. Samples that were cultured with excitotoxic agents but not IGF1 treatment exhibited severe loss of CtBP2/GluA2 double-positive puncta. IGF1 treatment increased the number of CtBP2/GluA2 double-positive puncta **(F)**. **G.** IGF1 reduces cerebral infarct size. Post-stroke IGF1 treatment reduced infarct size in adult rats **(G)**. **H.** IGF1 affects the plasticity in the FC and AN/FC synapses following kanamycin-induced deafness (Kong et al., 2010). Ultrastructural changes and postsynaptic density (PSD) of the AN/FC synapse were investigated **(H')**. M represents mitochondria. SV represents synaptic vesicles. The rectangle represents PSD. Mitochondrial swelling in the FC and AN/FC synapses was progressive until 28 days after kanamycin-induced damage **(H''-H''')**, whereas such ultrastructural changes in FC and AN/FC synapse disappeared afterward **(H''')**.


A
Created by modifying "schematic figure of the auditory neural pathway" (© Jonathan E. Peelle (Licensed under CC BY 4.0）) https://creativecommons.org/licenses/by/4.0/
Auditory cortex
Medial geniculate nucleus
Inferior colliculus
Nucleus of lateral lemniscus
Superior olivary complex
Dorsal acoustic stria
Intermediate acoustic stria
Ventral acoustic stria
AN
Cochlear nucleus
Plasticity
Regeneration
Protection
G
IGF1 treatment (-)
IGF1 treatment (+)
(Serhan *et al*, 2019)
H
without damage
1 day after deafness
28 days after deafness
140 days after deafness
M
AN
PSD
SV
FC
H'
H''
H'''
H''''
(Kong *et al*, 2010)
B
Cochlea
C
Tectorial membrane
outer HC
inner HC
Basilar membrane
Spiral ganglion cells
AN
Created by modifying "Organ of Corti" (© Madhero88 (Licensed under CC BY SA 3.0）) https://creativecommons.org/licenses/by/4.0/
Sensory epithelium
Protection (for HC)
E
IGF1 treatment (-)
IGF1 treatment (+)
Myosin7a/phalloidin
lateral
medial
outer HC
inner HC
(Yamahara *et al*, 2017)
D
inner HC
Cochlear ribbon synapses
Type I spiral ganglion neuron
Presynaptic ribbons
Post synaptic receptor pathchs
Spiral ganglion cells
Regeneration
Maitenance
F
IGF1 treatment (-)
IGF1 treatment (+)
Myo7a/CtBP2 /GluA2
Myo7a/CtBP2 /GluA2
(Yamahara *et al*, 2019)

impairment and HC loss (Iwai et al., 2006). To investigate the therapeutic potential of IGF1 in cochlear HCs, IGF1 was locally applied to guinea pig cochleae after noise exposure (Lee et al., 2007). IGF1 administration after noise exposure was found to attenuate HC damage functionally and histologically, as in the case of prophylactic administration, indicating the potential of IGF1 as a therapeutic agent against noise-induced SNHL. The effect of IGF1 on hearing preservation was also examined after cochlear implantation in guinea pigs (Yamahara et al., 2018). Cochlear implants (CIs) have become highly successful in restoring speech perception capacity in patients with profound SNHL. Although CIs have been previously indicated only for almost deaf patients, electric-acoustic stimulation (EAS) CI is indicated in patients with residual hearing at low frequencies. EAS CI provides electric and acoustic stimulation to compensate for high- and low-frequency sounds, respectively. However, the insertion of CI electrodes causes deterioration of residual hearing due to surgical trauma. To examine the effects on hearing preservation, IGF1 was applied to the round window membrane of guinea pigs at the time of electrode insertion. A previous study showed that local application of IGF1 preserves hearing ability for low-frequency sound after CI insertion (Yamahara et al., 2018). The mechanisms of HC protection by IGF1 have been evaluated using a cochlear explant culture system (Hayashi et al., 2013, 2014, 2017; Yamahara et al., 2017). In these studies, neonatal mice were used to establish explants, and aminoglycoside was used to induce damage in HCs (Fig. 1E). These studies showed that IGF1 maintains the HC number against aminoglycoside by inhibiting HC apoptosis and inducing supporting cell proliferation (Hayashi et al., 2013). Moreover, Netrin 1 might be an effector of IGF1 signaling during the maintenance of HCs damaged by aminoglycoside (Hayashi et al., 2014; Yamahara et al., 2017).

Based on the results of the animal experiments described above, clinical trials have been performed to study the efficacy of IGF1 for the treatment of sudden sensorineural hearing loss (Nakagawa et al., 2010, 2012, 2014), which indicated the safety and efficacy of local IGF1 application for the treatment of SNHL in humans.

Cochlear ribbon synapses

The cochlear ribbon synapses are vital structures present between the inner HCs and SGNs and are the first excitatory afferent synapses in the auditory pathway (Fig. 1D). Acoustic stimuli of various intensities and frequencies cause corresponding changes in the number, structure, shape, and function of the cochlear ribbon synapses. Therefore, cochlear ribbon synapses are critical components of auditory processing. These synapses are highly sensitive to noise, ototoxic drugs, and aging (Bharadwaj et al., 2014; Hickox and Liberman, 2014; Rodriguez-de la Rosa et al., 2017; Singer et al., 2018). Previous studies in animal models have shown that degeneration of cochlear ribbon synapses can occur prior to HC loss after noise trauma (Kujawa and Liberman, 2009). Other studies have indicated associations between the loss of cochlear ribbon synapses and difficulties in understanding speech in noisy environments (Bharadwaj et al., 2014), tinnitus (Hickox and Liberman, 2014; Rodriguez-de la Rosa et al., 2017; Singer et al., 2018), and hyperacusis (Hickox and Liberman, 2014). In age-related hearing impairment, loss of cochlear ribbon synapses has also been identified as one of the primary signs of degeneration (Sergeyenko et al., 2013; Viana et al., 2015). Cochlear ribbon synapses have limited spontaneous regenerative capacity (Maison et al., 2013; Wan and Corfas, 2015). Thus, cochlear ribbon synapses are important therapeutic targets for the treatment of SNHL.

Previous studies have investigated the potential of IGF1 for the maintenance and regeneration of cochlear ribbon synapses using cochlear organ cultures (Fig. 1F) (Yamahara et al., 2019; Gao et al., 2020). IGF1 promotes the regeneration of excitotoxic amino acid-induced damaged cochlear ribbon synapses (Fig. 1F) (Yamahara et al., 2019). The regenerative effects of IGF1 are attenuated by specific IGF1 receptor antagonists. IGF1 also contributes to the maintenance of cochlear ribbon synapses. Blocking of IGF1 signaling by a specific IGF1 receptor antagonist results in the reduction of ribbon synapses. After washout of a specific IGF1 receptor antagonist, the number of cochlear ribbon synapses spontaneously recovers , indicating that paracrine or autocrine systems of IGF1 in the cochlea play a crucial role in the maintenance of cochlear ribbon synapses after birth. Overall, these studies suggest that IGF1 can act as a therapeutic molecule for the targeting of cochlear ribbon synapses.

Interestingly, hearing recovery in patients with sudden SNHL after IGF1 treatment was observed approximately 4 weeks later. Their hearing exhibited a gradual improvement over time (Nakagawa et al., 2010, 2012, 2014). This suggests the involvement of regenerative events rather than the protection of HCs. Thus, the regeneration of cochlear ribbon synapses could be included in the mechanisms of hearing recovery in patients with sudden SNHL who received topical IGF1 application.

Auditory nerve and central nervous systems

Central hearing loss is caused by lesions in the central auditory pathway or the auditory cortex. The auditory cortex, located on the transverse temporal gyri of Heschl, processes and interprets sounds that are amplified and received by the cochlea.

Stroke in the temporal lobes causes central hearing loss (Akiyoshi et al., 2021). Thus, protecting neurons or reducing infarct size is essential for the restoration of hearing after cerebral infarction. No previous studies have investigated the effects of IGF1 on hearing

recovery after cerebral infarction, but IGF1 is shown to be a factor in post-injury neural and axonal regeneration over the past quarter of a century (Kanje et al., 1989; Sjöberg and Kanje, 1989; Nachemson et al., 1990). Serhan et al. reported that post-stroke systemic injections of IGF1 exert neuroprotective effects in rats (Fig. 1G) . In the study by Serhan et al., post-stroke IGF1 treatment reduced infarct size by 38% in adult rats, which resulted in a significant improvement in sensorimotor function following stroke (Fig. 1G). It has also been demonstrated that serum levels of IGF1 are positively correlated with clinical outcomes in stroke patients (Saber et al., 2017; Åberg et al., 2018). Thus, the application of IGF1 may be efficacious for hearing recovery in patients with central hearing impairment caused as a result of cerebral damage.

Moreover, another study revealed that IGF1 might affect reparative plasticity in the cochlear nucleus of kanamycin-induced deaf guinea pigs (Fig. 1H). Damage to the peripheral auditory system, especially HCs, causes retrograde degeneration of the SGN and AN, resulting in profound changes in the structure and function of the central auditory system (Spoendlin, 1975; Syka, 2002; Ramekers et al., 2020). The cross-sectional area of large spherical cells in the cochlear nucleus of gerbils was gradually reduced after removing the input to the cochlear nucleus as a result of damage to the cochlea (Pasic and Rubel, 1989). Kong et al. investigated the time course of deafness-induced plasticity in fusiform cells (FCs) and AN synapses on FC (AN/FC synapses) in the dorsal cochlear nucleus of guinea pigs following chronic kanamycin-induced deafness. Ultrastructural changes in the FC and AN/FC synapses were observed, and local *Igf1* mRNA extracted from the dorsal cochlear nucleus was quantified for 140 days after kanamycin treatment. Mitochondrial swelling in the FC and AN/FC synapses was progressive for 28 days after damage, whereas such ultrastructural changes in the FC and AN/FC synapses disappeared afterward (Fig. 1H), which suggests that FC and AN/FC synapses revived and remodeled themselves after deafferentation due to kanamycin. Interestingly, the upregulation of *Igf1* mRNA in the dorsal cochlear nucleus was persistent shortly after ultrastructural changes in the FCs and AN/FC synapses for 28 days after damage, whereas local *Igf1* mRNA was restored to the normal level once the ultrastructural changes were absent. These findings suggest that local IGF1 plays a role in deafness-induced plasticity in the FC and AN/FC synapses following chronic kanamycin-induced deafness (Kong et al., 2010).

Future studies are warranted to elucidate the effects of IGF1 on central neural hearing loss.

Possible use of IGF1 for age-related hearing loss

Age-related hearing loss (ARHL) is one of the most common chronic conditions and is the most prevalent chronic sensory deficit experienced by older adults. ARHL causes functional declines in auditory function, a loss of hearing sensitivity, beginning with high pitches or frequencies, and the inability to understand speech, particularly in the presence of background noise, thus topping the list of perceptual difficulties that are characteristic of old age (Frisina and Frisina, 1997).

It is now established that ARHL is a multifactorial disorder with numerous contributing risk factors, including extrinsic factors (noise, exposure to environmental ototoxic agents, trauma, vascular insults, metabolic changes, hormones, and diet), superimposed on an intrinsic, genetically driven, and physiologic aging process (Fetoni et al., 2011; Yamasoba et al., 2013). Studies in humans and animals have revealed that many structural changes occur in the peripheral and central auditory regions in ARHL (Yamasoba et al., 2013; Frisina et al., 2016; Profant et al., 2020; Wu et al., 2020), which include degeneration of the HCs, stria vascularis, ANs, and central auditory pathways (Fetoni et al., 2011; Yamasoba et al., 2013; Rodriguez-de la Rosa et al., 2017; Profant et al., 2020). Therefore, most cases of ARHL exhibit a mixture of peripheral and central abnormalities (Gates and Mills, 2005).

There are some studies on the relationship between IGF1 and ARHL. In humans, IGF1 levels are highest during puberty, which then decline with age (Gomez, 2007). An epidemiologic study of aging cohorts showed a relationship between IGF1 and hearing loss (Lassale et al., 2017). This study revealed that decreased age-related-IGF1 bioavailability correlates with the progression of hearing impairment, showing the possibility that higher levels of IGF1 confer some protection against ARHL (Lassale et al., 2017). Investigating Laron's syndrome (OMIM#262500) may also help elucidate the relationship between IGF1 and ARHL. Laron's syndrome is an autosomal recessive human disorder characterized by mutations in the growth hormone receptor that cause insensitivity to growth hormone stimuli and, in turn, extremely low IGF1 synthesis in the liver (Laron, 1999). Almost all patients have normal hearing levels at a young age (Chernausek et al., 2007) but develop early-onset ARHL (Attias et al., 2012). Interestingly, hearing impairment in Laron's syndrome is prevented by treatment with IGF1 at an early developmental stage, whereas patients who started treatment late experienced various degrees of SNHL (Attias et al., 2012). Long-term treatment with IGF1 is reportedly associated with adverse effects, such as hypoglycemia or tonsillar/adenoidal hypertrophy (Chernausek et al., 2007). However, the available data highlight the interest of investigating IGF1 as a drug candidate for ARHL.

Other peripheral nervous systems

Previous studies have shown that IGF1 acts on the nervous system in several different ways by promoting the development and growth of neurons and glial cells, along with differentiation of Schwann cells and their

migration to axons, neurite outgrowth, and neuronal survival (Rabinovsky, 2004; Xiang et al., 2011). In addition to auditory systems, IGF1 also has the potential as a therapeutic molecule for other peripheral nervous systems.

Olfactory system

The olfactory system consists of peripheral compartments, such as the olfactory mucosa, which consists of the olfactory epithelium and lamina propria, and central structures such as the olfactory bulb, piriform, or orbitofrontal cortex. The olfactory epithelium (OE) is composed of layers of supporting cells, olfactory receptor neurons (ORNs), and basal cells (Fig. 2A-B'). There are two distinct types of basal cells: horizontal basal cells and globose basal cells. The first step in olfaction is the binding of odorant molecules to odorant receptors in the chemosensitive cilia of ORNs. Olfactory signals from ORNs relay to second-order neurons, such as the mitral cells in the olfactory bulb. The ORNs and mitral cells form synapses, forming signal-processing modules (glomerulus). Second-order neurons extend their axons along the lateral olfactory tract toward the piriform and orbitofrontal cortices. The OE has a unique regenerative stem cell system, which is maintained by the life-long replenishment of mature ORNs from globose basal cells (Farbman, 1990). Globose basal cells continuously differentiate into neuronal progenitors and then differentiate into immature ORNs. Various stimuli, such as cytokines and growth factors, induce the differentiation and maturation of ORNs (Hansel et al., 2001; Kondo et al., 2020). However, this ability of OE decreases with aging and/or various toxic factors, including environmental chemicals (cigarettes, etc.), upper respiratory tract infection, and trauma, leading to olfactory impairment (Ueha et al., 2016; Hummel et al., 2017; Kondo et al., 2020).

Several studies have investigated the association between IGF1 and the olfactory system (Pixley et al., 1998; Ueha et al., 2016, 2018a,b). *Igf1* is expressed at high levels in the OE and olfactory bulb (Bondy and Lee, 1993; Ueha et al., 2018b). In aged OE, reduced expression of *Igf1*, ORN numbers, and cell proliferation are observed, which contribute to olfactory impairment during aging (Ueha et al., 2018b). The effect of IGF1 administration on intact animals was investigated, with results showing that IGF1 promotes the generation and survival of ORNs in newborn rats . The effect of IGF1 on age-induced negative effects on ORNs has been investigated. IGF1 was subcutaneously administered to aged mice, and IGF1 administration increased the number of olfactory progenitors, immature ORNs, and mature ORNs in the OE. Additionally, Fukuda et al. studied the effect of IGF1 on the degenerated OE of aging mice induced by methimazole. Immediately after the administration of methimazole, the whole OE degenerated, and only the basal cells remained. Intranasal administration of IGF1 in gelation hydrogel was performed, and the results showed that IGF1 stimulated basal cells, leading to an increase in the number of mature ORNs and thickness of OE (Fukuda et al., 2018).

Facial nerve

The facial nerve controls the muscles used for facial expressions, and the loss of such function leads to aesthetic and emotional problems. As a neurotrophic factor, IGF1 is involved in the recovery of peripheral facial nerves (Kiryakova et al., 2010; Seitz et al., 2011; Bayrak et al., 2017;, Raimondo et al., 2019; Sugiyama et al., 2020; Kimura et al., 2021). Marked *Igf1* and *Igf1r* mRNA upregulation 2 days after facial nerve injury was detected in the proximal nerve stump using reverse transcription-PCR and confirmed using immunohistochemistry for IGF1 and IGF1R (Streppel et al., 2002; Angelov et al., 2005). The effect of IGF1 on the recovery of facial nerve crush injury was evaluated in guinea pig and rabbit models (Bayrak et al., 2017; Sugiyama et al., 2020; Kimura et al., 2021). In these studies, the facial nerve within the temporal bone was compressed by clamping or frozen. Compared with the control group, animals treated with local application of IGF1 showed a significant improvement based on the degree of eyelid closure, number or order of axons, and compound muscle action potential amplitudes of the crushed nerves (Bayrak et al., 2017; Sugiyama et al., 2020; Kimura et al., 2021). Additionally, some studies have revealed that IGF1 improves the accuracy of reinnervation and recovery of function (Kiryakova et al., 2010; Seitz et al., 2011). Generally, inaccurate reinnervation of muscle targets occurs after transection of the facial nerve, leading to poor recovery of facial nerve function (Sumner, 1990; Moran and Graeber, 2004). Kiryakova et al. found that manual stimulation of denervated whisker pads after facial nerve injury reduces the amount of terminal sprouting; more accurate reinnervation patterns are associated with improved whisking function and blink reflexes (Bischoff et al., 2009; Kiryakova et al., 2010). Interestingly, when IGF1 is administered, manual stimulation improves the accuracy of reinnervation and recovery of function, such as muscle power, motor evoked potentials, and conduction velocity (Welch et al., 1997; Lutz et al., 1999; Kiryakova et al., 2010; Seitz et al., 2011). Raimondo et al. investigated the effect of IGF1 on functional innervation and improvement of craniofacial muscle transfer, which is the gold standard for reanimation following chronic facial palsy (Raimondo et al., 2019). Raimondo et al. used a rabbit model of craniofacial muscle transfer to the facial nerve. The gracilis muscle was transferred, and hydrogels containing IGF1 and vascular endothelial growth factor were injected into the gracilis muscle before transfer (Raimondo et al., 2019). The results showed that functional innervation in the transplanted muscle occurred via a hydrogel source of growth factors (Raimondo et al., 2019).

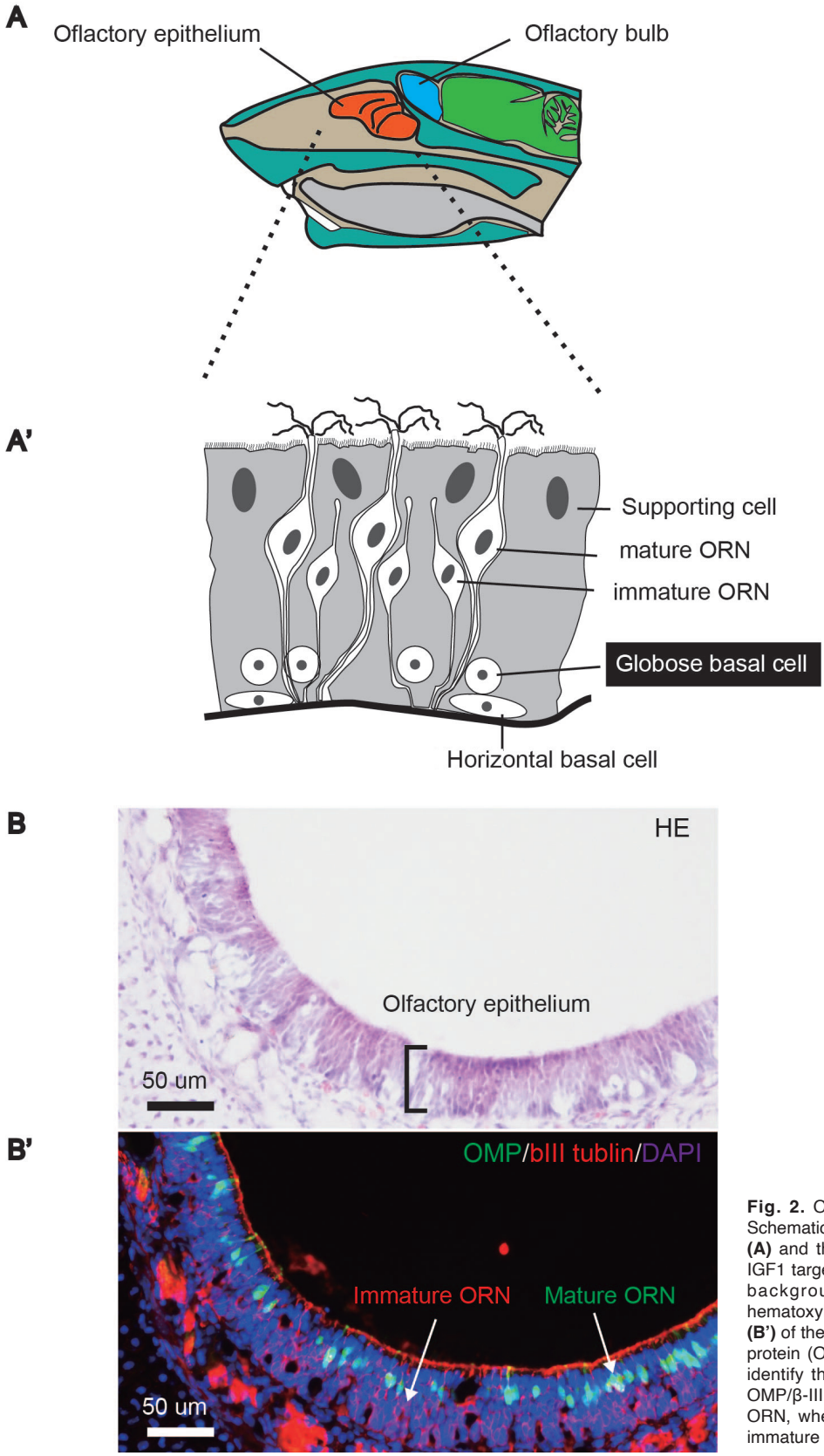


Fig. 2. Olfactory system and IGF1 targets. **A-A'.** Schematic of a sagittal view of the mouse nasal cavity **(A)** and the anatomy of the olfactory epithelium **(A')**. IGF1 targets are shown as white characters on a black background. **B-B'.** Representative images of hematoxylin and eosin **(B)** and immunohistochemistry **(B')** of the mouse olfactory epithelium. Olfactory marker protein (OMP), β-III tubulin, and DAPI were stained to identify the mature and immature ORN, respectively. OMP/β-III tubulin double-positive cells are the mature ORN, whereas β-III tublin-alone positive cells are the immature ORN. Scale bar represents 50 μm.

The available data highlight the importance of investigating IGF1 as a candidate drug for peripheral facial palsy. However, almost all studies used animal models of facial palsy produced by clamping or transection of the facial nerve. In a clinical setting, common causes of peripheral facial nerve palsy are Bell's palsy or Ramsay Hunt syndrome, which can occur as a result of neural edema and constriction within the facial canal. Thus, animal models of peripheral facial palsy produced by the same pathology as that of Bell's palsy or Ramsay Hunt syndrome are also needed to determine the clinical use of IGF1 for the treatment of facial palsy.

Conclusion

In this review, IGF1 was described as a novel and potent therapeutic agent for the treatment of the auditory system, olfactory system, and facial nerves. Animal studies have revealed that exogenous IGF1 has protective effects on the damaged auditory pathways, including HCs, cochlear synapses, and the central nervous system. In clinical trials, IGF1 is shown to be effective against SNHL. In addition, IGF1 bioavailability may be related to the progression of ARHL. IGF1 has regenerative effects on the damaged olfactory epithelium and facial nerves of animals. Further human research on IGF1 may contribute to the development of treatment methods that are additive to or more effective than currently available methods.

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