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VERSITA
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TARGETING THE SOMATOSTATIN RECEPTORS AS A THERAPEUTIC APPROACH FOR THE PRESERVATION AND PROTECTION OF THE MAMMALIAN COCHLEA FROM EXCITOTOXICITY

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Abstract

The neuropeptide somatostatin (SST) is an important modulator of neurotransmission in the central nervous system (CNS) and binds to G-protein-coupled receptors (SSTR1-5) on target cells. Little is known about the expression and function of the somatostatinergic system in the mammalian cochlea. We analyzed the expression of SSTR1-SSTR5 in the immature mammalian cochlea. The peak in the expression of SSTR1 and SSTR2 at mRNA and protein level is around the onset of hearing to airborne sound, at postnatal day (P)14. This suggests their involvement in the maturation of the mammalian cochlea. We demonstrated that all five receptors are expressed in the inner hair cells (IHC) and outer hear cells (OHC) as well as in defined supporting cells of the organ of Corti (OC) in the adult mouse cochlea. A similar expression of the SSTRs in the IHC and OHC was found in cultivated P6 mouse OC explants as well as in neuroepithelial cell culture. In order to learn more about the regulation of SSTRs, we used mice with either a deletion of SSTR1, SSTR2 or SSTR1/SSTR2 double knock out (DKO). In DKO mice, SSTR5 was up-regulated and SSTR3 and SSTR4 were down regulated. These findings provide evidence of a compensatory regulation in the mammalian cochlea as a consequence of a receptor subtype deletion. In addition, we observed reduced levels of phospho-Akt and total-Akt in SSTR1 KO and DKO mice as compared to wild type (WT) mice. Akt is likely to be involved in hair cell survival. Most importantly, we found improved hair cell survival in somatostatin and octreotide treated OC explants that had been exposed to gentamicin compared to those explants exposed to gentamicin alone. These findings propose that the somatostatinergic system within the cochlea may have neuroprotective properties.

Keywords

• Cochlea • Hair cells • Knockout mice • Organ of Corti • Somatostatin receptor

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Introduction

Somatostatin (SST), a regulatory peptide with two bioactive forms, SST-14 and SST-28, is produced in neuroendocrine cells in the brain and periphery and acts on a wide array of tissue targets to modulate neurotransmission, cell secretion, and cell proliferation [1]. The discovery of somatostatin receptor subtypes triggered in depth research into their binding properties and coupling to multiple signaling pathways. SST acts via a family of G-protein-coupled receptors (SSTR1-SSTR5), which are differentially distributed throughout the central nerve system (CNS) [2,3]. Signaling through somatostatin receptors is complex and involves auto-, para-, or endocrine mechanisms [4]. Based on their sequence homology, the receptor subtypes can be placed into two subgroups. The classification is based on structural features and strongly supported by their pharmacological properties. The first receptor group comprises SSTR2, SSTR3 and SSTR5 while SSTR1 and SSTR4 belong to the second group.

The studies published are broadly in agreement and suggested that all the SST receptor types are widespread throughout the brain [5]. The five SSTRs are variably expressed in the brain. In the rat, mRNA for SSTR1 is the most abundant followed by SSTR2, SSTR5, SSTR3 and SSTR4 [1]. In mammalian, all five subtypes of SSTRs are expressed also in the retina. They are distributed to specific retinal cell populations, including subtypes of photoreceptor, bipolar, amacrine and ganglion cells [6]. Most SSTR subtypes have been shown to modulate voltage-gated Ca^{2+} channels as well as glutamate receptor channels in several organ systems [7,8]. Excessive Ca^{2+} influx into cells is thought to be a major contributor to cell death in ischemic and excitotoxic models of neuronal injury [8,9]. Binding of somatostatin to its receptors induces G-protein activation through various pathways. As a consequence, the activation of several key enzymes, including adenylyl cyclase, phosphothyrosine phosphatase (PTPase) and mitogen activated protein kinase (MAPK) are modulated along with changes in the intracellular levels of calcium and potassium ions [10,11]. Studies over the last few years in mice show that SST and its receptors appear to play an important role in cell death [12,13]. However, in contrast to the situation in the brain and retina, only little information is available on the expression or function of SST and its receptors in the inner ear and auditory system. Tachibana at el. reported on SST-like immunostaining in the medial geniculate body, cochlear nucleus,

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inferior colliculus, auditory cortex and in the cochlea [14]. Tachibana did not find SST-like immunostaining in the cochlear perilymph. Also, SST-like immunostaining could be observed in the cochlear nuclei of postnatal rats and it was suggested that somatostatin might be important for the development of the auditory system [15]. In an additional study, SST producing cells could be observed in the covering epithelium of the spiral prominence and in the epithelium of the intermediate and rugosal part of the endolymphatic sac [16].

In recent studies from our group, we demonstrated expression of SSTR1 and SSTR2 mRNA in the postnatal rat cochlea and we reported on a dose-dependent protective effect of somatostatin on gentamicin-induced HC loss in vitro [17].

The present review will focus on the relevant aspects of SSTRs expression during development and in the mature mouse cochlea. In addition, it provides information concerning recent and unpublished data from our laboratory, in particular focusing on recent studies using cochlea of mice carrying genetic deletion of the SSTR1, SSTR2 and deletion of both SSTR1 and SSTR2 as experimental models. Finally, the evidence will be reviewed supporting a possible role of SST in maturation of the cochlea and for the hearing process.

Somatostatin and localization of somatostatin receptors in the mammalian cochlea

Many studies suggested that all SSTRs types are widespread throughout the brain and are variably expressed in the brain. In the rat, [18]. The distribution of the mRNA expression for all five SSTRs types has been investigated extensively using different technique in the rat and human [19]. At present, very little is known about the expression of SSTRs receptors in the inner ear.

During maturation of the hearing organ, SSTR1 and SSTR2 were expressed in cochlea during late embryonic development. In the period of cochlear extension and coiling (until approximately E19-P0) the expression of SSTR1 and SSTR2 receptors increased and continued throughout the maturation of OC [20]. The high expression of both receptors at E17 supports the differentiation of the neuroepithelial cells in the embryonic OC, as well as general growth and development of the inner ear (Figure 1). A variety of studies support a developmental role for SST by documenting its early onset, transient expression, and morphogenetic effects [21]. Transient expression of SST protein or mRNA has been described in the cerebellum [22], the cerebral cortex [23], and in sensory systems, including the somatosensory, visual [24], and auditory systems [25]. Recent studies have shown that SST exerts some regulatory effects during neuronal maturation, as it has been reported that SST enhances neurite outgrowth in cultured cerebellar neurons [26]. In the postnatal period of cochlear development the immunostaining of both receptors increases until approximately P14 at the onset of hearing. During this postnatal period maximal labeling of the IHC, OHC, and supporting cells is reached for both receptors, and subsequently decreases by P21 [20]. SST is also known to modify the synapses and is likely to influence the synaptic activity of the inner ear at P14 [27]. Like other rodent species, mice do not respond to airborne sound shortly after birth. The outer ear canal remains closed until P12, and auditory brainstem responses cannot be reliably recorded before P12-P14 [28]. The increase of these proteins until P14 may be necessary for the growth and development of the OC, although not for mature hearing. In addition, it is noteworthy that the developmental pattern

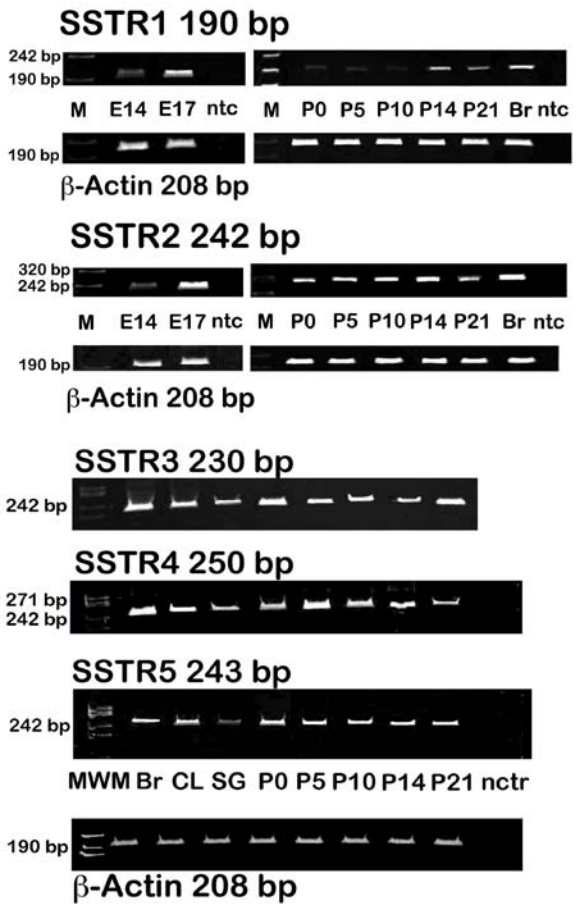

Figure 1. Gene expression of SSTR1-5, in the in the OC explants at different embryonic and postnatal ages. All five receptors mRNA was detected in the OC of wild-type mice by RT-PCR with the use of specific primer sets at E14, E17 and P0, P5, P10, P14, and P21. Gene expression of SSTR3, 4 and 5, was also detected in the cell lysate (CL) of neuroepithelial cells, spiral ganlion SG and Brain (Br), which RNA was used as a positive control. Omission of RT-PCR was used as the no template control (ntc). β-actin was used to control cDNA synthesis. Molecular weight marker (MWM).

of SSTR1 and SSTR2 expression are similar to each other. Interestingly, there is a strong correlation of mRNA and protein levels for both SSTR1 and SSTR2 receptor, suggesting that SSTRs expression in the inner ear is controlled at the transcriptional level. The expression of SSTR1 and SSTR2 at P21 is decreased relative to P14. The distribution patterns of SSTR1 and SSTR2 at P21 were similar to those observed in adult mice after airborne hearing ability has commenced. From brain studies it is suggested that the SSTR1 and SSTR2 appear relatively early in the development. It has been suggested that during brain development SST may be involved in synaptogenesis, proliferation, axon pathfinding, and/or as a tropic factor [29]. Furthermore because of the high expression level of SSTR1 and SSTR2 in the cochlea at age P14 they may not only be involved in proliferation but also in synaptogenesis.

Our recent observation in mouse cochlea show that all SSTRs were expressed mRNA and protein level. In the cochlea of adult mice SSTR1 immunorecativity was observed in apical part of the OHC and IHC, inner PiC, and spinal ganglion (SG) (Figure 2B) [30]. SSTR2 immunoreactivity was observed in the IHC and OHC with strong intensity in the supporting cells (Pillar`s and Deiter`s cells) (Figure 3A)(Table 1A). According to the labeling with neurofilament marker SMI3, the cochlear afferent neurons do not expressed SSTR1 and SSTR2 [30].

Furthermore, in our studies we demonstrate that the SSTR3-5 are specifically expressed in OHC and IHC of the OC, as well as in defined supporting cells (Figure 3). Expression of SSTR3 in adult mouse cochlea with prominent immunostaining was detected in the basal part of OHC, apical part of IHC as well as in cell bodies of SG cells (Figure 3B) (Table 1B). The SSTR3 immunoreactivity was widely distributed throughout the human bran, being particularly enriched in the cortex, hippocampus, the amigdala, the hippothalamus and cerebellum [31]. Analysis at the fluorescence microscopic level revealed and exclusive localization of SSTR4 at supporting cells of OHC. Also strong signal was detected at the apical part of IHC (Figure 3C). The SG shows a strong signal in the cell body of all type of ganglion cells. Immunohistochemistry on adult rat brain section showed the SSTR4

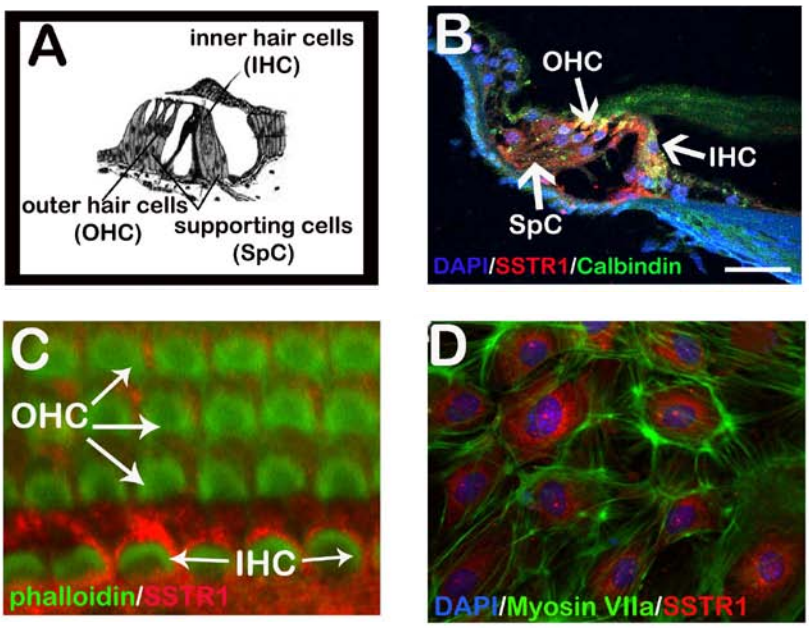

Figure 2. Localization of SSTR1 receptor in the adult mouse cochlea, OC explants and in passaged neurosensory cell by immunocytochemistry. A. The diagram of OC source: http://syllabus.med.unc.edu. B. Localization of SSTR in mouse cochlea. Cell nuclei are in blue (DAPI), SSTR1 in red. SSTR1 can be detected in OHC,and IHC as well as in supporting cells. C. Expression of SSTR1 in OC explants. Phalloidin staining in green and SSTR1 in red. Immunoreactivity signal of SSTR1 receptor was stronger in IHC than in OHC of OC (arrow). D. Expression of SSTR1 in passaged neurosensory cell. Cell nuclei are in blue, the HC marker myosin VII in green and SSTR1 in red. SSTR1 can be detected perinuclear in the cells. Images by immunofluorescence microscopy. Scale bar = 100 µm

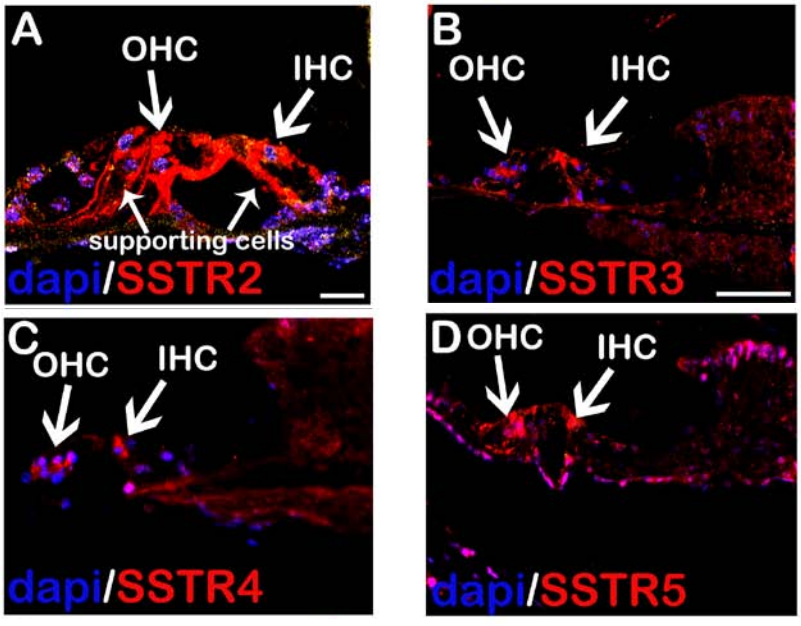

Figure 3. The protein expression profile of SSTR3, 4 and 5 in the adult mouse cochlea. A. SSTR2 (red) can be detected in OHC, IHC and with the strong signal in supporting cells. B. The protein expression of SSTR3 (red) in the OC can be detected in IHC and OHC included the supporting cells of OHC; cell nuclei (DAPI) are in blue. C. SSTR4 immunolabeling was prominent in the supporting cells of OHC but was also detected in the IHC and OHC. D. SSTR5 immunolabeling in the mouse cochlea was in the OC and SG. Strong signal of SSTR5 was detected in IHC and OHC. All images by immunofluorescence microscopy, scale bar = 100 µm

Table 1. Regional distribution of SSTR1-5 in the mouse cochlea determined by immunohistochemistry. The table lists relative densities of SSTRs signals in cochlear structures.

A

	SST1 Immunoreactivity							SST2 Immunoreactivity					
	Embryonic OC	Supporting cells	IHC	OHC	PiC	DeC		Embryonic OC	Supporting cells	IHC	OHC	PiC	DeC
E14	+	++					E14	++	+++				
E17	+++	++					E17	+++	+				
P0			+++	+++	+	+	P0			+++	+++	++	++
P5			++	++	++	++	P5			++	+++	++	++
P10			++	+++	+++	+++	P10			++	+++	+++	+++
P14			+	+	+++	++	P14			++	+++	++	+++
P21			+	+	+	+++	P21			+	+	++	+++

+ weak, ++ moderate, +++ strong

B

SSTR1-5 Immunoreactivity				
	Area			
SSTRs	IHC	OHC	PiC	DeC
SSTR3	+++	++	++	+++
SSTR4	++	+	+	+++
SSTR5	+++	+++	+	++

+ weak, ++ moderate, +++ strong

to have a common distribution in cell body as well as neuronal processes in the cerebral cortex, hippocampus and several nuclei in the brainstem [32]. The study of Schreff et al. showed that SSTR4 was strictly somatodendritic and most likely functions in a postsynaptic manner. The SSTR4 may have a previous unappreciated function during the neuronal degeneration-regeneration process [33]. SSTR5 immunoreactivity showed an overall distribution in OC with strong immunostaining in the apical and basal part of OHC and apical part of IHC (Figure 3D). SSTR5 was prominent expressed in the basal forebrain, suggesting that they may be involved in the mediation of somatostatin effects on the sleep-wake cycle through their association with cortically projecting subcortical systems [34]. All five subtypes of SSTRs are expressed in the mammalian retina. There are distributed to specific retinal cell population, including subtypes of photoreceptor, bipolar, amacrine and ganglion cells [6].

The expression of SSTR1-and 2 in cultivated P5 mouse OC explants was similar to their expression in IHC and OHC (Figure 2C). A similar expression of the SST receptors in the inner and outer hair cells was found in cultivated P6 mouse OC explants and in cultivated neurosensory cells (Figure 2D) [30]. Somatostatin itself was not expressed in the mammalian cochlea, suggesting that somatostatin reaches its receptors either through the blood-labyrinthine barrier from the systemic circulation or via the endolymphatic duct from the endolymphatic sac [30].

Expression of somatostatin receptors in cochlea of knock out mice

The KO and DKO mice in which SSTR1 and SSTR2 are knocked out have been generated and used to investigate the biological consequences of the absence of SSTRs [35]. These KO and DKO do not exhibit major phenotypic defects or main behavioral impairments [36]. Immunohistochemisty in SSTR1 KO cochlea shows that SSTR2 was increased in SSTR1 KO mice. SSTR2 protein was strongly expressed in DeC, and to a lesser extent in OHC, but was absent from PiC and IHC compared with WT mice. In SSTR2 KO the staining pattern did not differ from that of WT mice [30]. In addition, no major compensatory regulation of SST or individual SSTRs has been described as a consequence of the genetic deletion of SSTR1 or SSTR2 in specific brain regions [37]. In the retina, recently major alterations of SST content were demonstrated as a consequence of SSTR1 or SSTR2 deletion [38]. Indeed, SSTR1 loss causes an increased expression of SSTR2 [30]. In the DKO mouse cochlea the expression of SSTR3 mRNA, as measured with quantitative qPCR in OC explants from P21 day-old mice was not significantly changed but the expression of SSTR4 in OC explants from P21 day-old mice was significantly decreased compared to age matched OC explants from WT mice. SSTR5 mRNA was expressed at a significantly higher level compared to WT cochlea (Figure 4). Our findings demonstrate prominent compensatory regulation in the mammalian

cochlea as a consequence of distinct SSTRs deletions. This compensatory mechanism is subtype-specific, as it is observed only after the deletion of SSTR1, SSTR1/SSTR2 but not after the deletion of SST2 [30].

Role of somatostatin in protecting the inner ear

The function of these five receptors in the OC is currently unknown. However, we have recently demonstrated that SST can protect HCs from aminoglycoside toxicity in a dose-dependent manner in vitro [17]. Protective effect was also seen in the treatment with somatostatin analogue octeotride (Figure 5A). Decreased hair cell loss in octreotide-treated samples that had been exposed to gentamicin provides evidence for a protective effect of octreotidein aminoglycoside-induced hair cell death in vitro. (unpublished data).

It is reasonable to assume that this neuroprotective effect of SST on HCs was mediated by SSTRs; however, this has not yet been experimentally proven. Nevertheless, our findings are consistent with a neuroprotective role for the SST signaling system with respect to auditory HCs. In contrast to the situation in the inner ear, more is known about the expression and neuroprotective role of the somatostatinergic system in the retina. It has been demonstrated that SST and its receptors (SSTR1-SSTR5) are expressed in the retina, predominatly in amacrine cells and bipolar cells [39]. Activation of the SSTR2 by somatostatin or its analogues has been shown to protect retinal neurons against ischemia-induced damage [7]. In addition, studies in mice with genetic alterations of the somatostatinergic system have revealed that an increased presence of functional SSTR2 protects against retinal ischemia. Therefore, SSTR2 analogues might be of therapeutic benefit in retinal diseases such as glaucoma or diabetic retinopathy, but may also protect from hearing loss due to HC degeneration and death. Studies in mouse retinal explants have demonstrated that the SSTR2 receptor inhibits potassium-induced glutamate release [40]. By limiting the amount of glutamate available to glutamate receptors, somatostatin and its analogues may exert a neuroprotective function against glutamate neurotoxicity, which characterizes many retinal diseases [41]. Glutamate excitotoxicity appears to be mediated by the activation of caspase-3, as shown in cortical neurons [42]. Glutamate excitotoxicity is also involved in HC damage and death in the cochlea [43]. Therefore, somatostatin may protect HCs from aminoglycoside toxicity, either by limiting glutamate release or by mitigating the toxic action of excess glutamate on HCs. In this context, it is notable that the somatostatin analogue octreotide alters the activity of the phosphatidylinositol 3-kinase pathway in pituitary tumor cells [44]. We demonstrated recently that the phosphatidylinositol 3-kinase pathway is involved in NF-kappaB-dependent HC survival [45]. Therefore, it might be possible that somatostatin exerts its effect on HCs through the phosphatidylinositol 3-kinase survival pathway. Our analysis of levels of phospho-Akt and total Akt protein in WT, SSTR1 KO, and DKO mice demonstrated that deletion of the receptors results in reduced levels of phospho- Akt and total Akt in the KO mice compared with WT mice (Figure 5B) [20]. Therefore, we can speculate that the protective role of SST on gentamicin-induced HC loss is due to the influence of SST at the PI3K/Akt pathway.

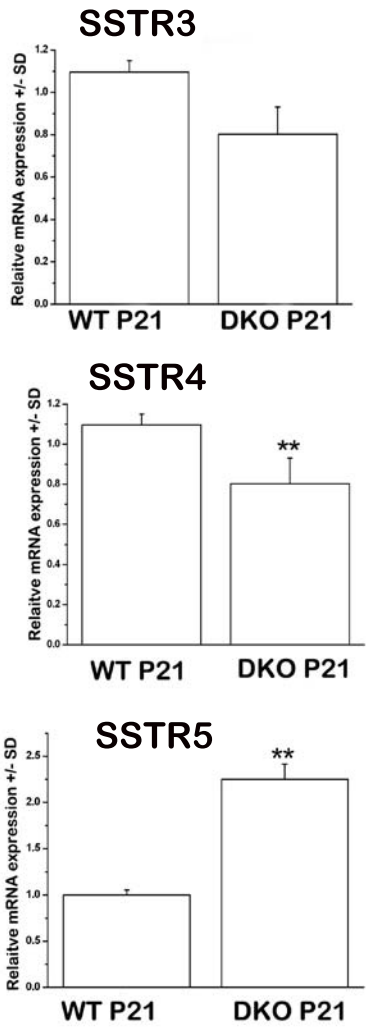

Figure 4. SSTR3, 4 and 5 cochlear gene expression in OC explants P21 of wild type and DKO mice. The relative distribution of SSTR3, 4 and 5 mRNA expression in OC tissue from wild-type and DKO mice of different postnatal ages was quantified by real-time PCR. GAPDH was used as an endogenous control. Gene expression levels are expressed as mean (± S.E.) fold increase as compared with values obtained in OC explants from P21 mice from WT and DKO. Data were obtained from 5 independent experiments. Statistical analysis was performed using the student t-test. ** $p<0.004$.

Conclusions

In this review we have presented evidence for complex mechanisms by which the expression of the SSTRs in the highly differentiated cochlear tissue is closely interrelated. SSTRs are expressed in cochlea during late embryonic development. In the period of cochlear extension the expression of SSTR1 and SSTR2 receptors increased and continued throughout the maturation of OC. Our studies support a developmental role for SST by documenting its early onset, expression, and morphogenetic effects. The presence of SSTR1-5 within the mammalian cochlea, their specific expression in the OC, and their subtype-specific compensatory regulation as a consequence of distinct somatostatin receptor deletion suggest an important role for the somatostatinergic system within the inner ear. Additional studies are needed to clarify to what extent SSTR play an essential role during the development of cochlear neural structures, and which transduction mechanisms are involved given the activation of specific SST receptor subtypes.

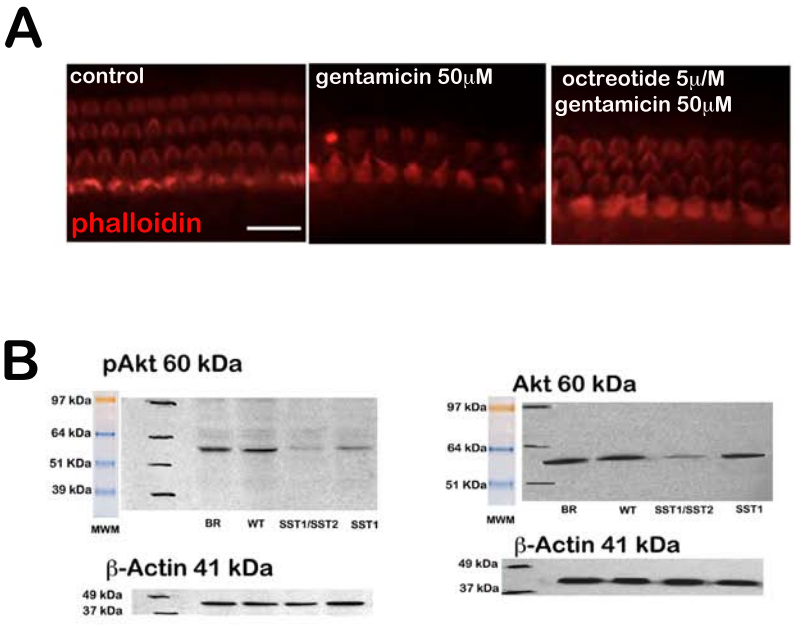

Figure 5. Effect of somatostatin anloge octrotide on gentamicin-induced hair cell damage.
A. Photograph of phalloidin-labeled OCs (red). Control: Untreated OCs demonstrate three orderly rows of OHC and a single row of IHC. Gentamicin treated: OCs cultured with gentamicin showed significant loss of hair cells. Octreotid treated: Treatment with 5 μM of octreotide in addition to gentamicin resulted in significant decrease in hair cells loss compared with gentamicin treatment only.
B. Detection of total and phospho Akt in OC of SSTR1 KO, SSTR1/SSTR2 KO as well as in the brain. Levels of both phospho-Akt and total-Akt were reduced in SSTR1 and SSTR1/SSTR2 KO mice compared to the wild-type littermates. The brain served as positive control. β-actin levels were used as loading controls. Images by immunofluorescence microscopy. Scale bar = 100 μm (A)

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