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The Role of Glucocorticoids for Spiral Ganglion Neuron Survival

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Abstract

Glucocorticoids, which are steroidal stress hormones, have a broad array of biological functions. Synthetic glucocorticoids are frequently used therapeutically for many pathologic conditions, including diseases of the inner ear. Despite their use, their exact functions in the cochlea are not completely understood. Recent work has clearly demonstrated the presence of glucocorticoid signaling pathways in the cochlea and their protective roles against noise-induced hearing loss. Furthermore, indirect evidence suggests the involvement of glucocorticoids in age-related loss of spiral ganglion neurons and extensive studies in the central nervous system have demonstrated profound effects of glucocorticoids on neuronal functions. With the advancement of recent pharmacological and genetic tools, the role of these pathways in the survival of spiral ganglion neurons after noise exposure and during aging should be revealed.

Keywords

glucocorticoid; hair cell; spiral ganglion neuron; age-related hearing loss; noise-induced hearing loss; corticosteroid

1. The signaling pathways for glucocorticoids

To survive in a challenging environment, most complex organisms have evolutionarily developed a stress response system. In humans and other vertebrates, the adrenal steroid glucocorticoids (GCs) modulate and control this system at multiple levels (see recent reviews, Kino, 2007; Viegas et al., 2008). Synthetic GCs are currently widely used to treat allergic, inflammatory, and lymphoproliferative disorders as well as hearing loss in a variety of inner ear diseases such as Meniere's disease, sudden or idiopathic hearing loss, endolymphatic hydrops and autoimmune inner ear disease (Dodson and Sismanis, 2004; Dodson et al., 2004; McCabe, 1979; Trune et al., 2007; Wei et al., 2006). Despite their wide use, the role of GC signaling pathways in the inner ear is poorly understood.

Using cholesterol as the starting molecule, the adrenal cortex secretes three types of steroid hormones: 1) GCs (cortisol in humans and most other mammals, and corticosterone in rodents

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and lower vertebrates), 2) mineralocorticoids (MCs) such as aldosterone, and 3) androgens including dehydroepiandrosterone, a precursor of testosterone (Payne and Hales, 2004). The level of GCs is regulated by the secretion of adrenocorticotrophic hormone from the pituitary, which in turn is regulated by arginine-vasopressin and corticotrophin-releasing hormone from the hypothalamus. This regulation system is called the hypothalamic-pituitary-adrenal (HPA) axis, to which GCs can act on in a negative feedback loop (Smith and Vale, 2006). GCs, as small hydrophobic compounds, travel in serum mostly by the carrier protein corticosteroid-binding globulin. Upon reaching the target cells, GCs mediate their biological responses mainly through the glucocorticoid receptor (GR) and - in certain tissues - through the mineralocorticoid receptor (MR), which have a much higher affinity for GCs than GR. As both receptors are present in spiral ganglion neurons and other cell types in the cochlea, we will discuss the signaling pathways initiated by both GR and MR.

1.1. GR signaling pathways

Only one gene is known to encode GR. It is located on chromosome 5q31-q32 and produces two major GR isoforms by alternative splicing of its nine exons (Stolte et al., 2006). The GR α isoform is expressed in almost all cells and is fully functional after binding to GCs, while the GR β isoform accounts for only 0.2-1.0% of total GR expression and does not bind GCs. Thus, we focus on the GR α isoform (simplified as GR) in the rest of this review. The structure of GR comprises of: (a) an N-terminal domain containing the transactivation function-1 (AF-1) region - a highly conserved DNA-binding domain (zinc-finger motif), (b) a C-terminal domain that binds ligands (AF-2) and (c) a protein-protein interaction region. In the cytoplasm, the unligated GR forms a multiprotein complex with chaperone proteins (hsp90 and hsp70), immunophilin p59, co-chaperone phosphoproteins (p23 and Src), and several kinases of the mitogen-activated protein (MAP) kinase signaling pathways. GRs can exert their effects via genomic and nongenomic pathways. In the genomic pathway (Figure 1), the binding of GCs to GR in the cytoplasm results in GR dissociation from the multiprotein complex. GR then dimerizes and translocates into the nucleus within 10-30 minutes after binding GC. The activated GC-GR complex modulates gene expression by direct interactions with the specific GC response elements (GREs) of target genes. While the AF-1 region interacts directly with transcription factors and many other cofactors, AF-2 must undergo a GC-dependent conformational change before interacting with coactivators or corepressors. Thus, the GC-GR complex can either activate (transactivation) or inhibit (transrepression) gene expression in different contexts. Monomers of the GC-GR complex can also interact with other transcription factors such as nuclear factor- κ B (NF- κ B), activator protein 1 (AP-1), and STAT5, representing another genomic pathway mechanism of action by GCs (Beato and Sanchez-Pacheco, 1996; Datson et al., 2008; Xu et al., 2009). The binding of the GC-GR monomer to these transcription factors can prevent their association with DNA, or compete with them for nuclear coactivators, both leading to reduced transcription. However, this GR genomic pathway is also cell-context dependent. For example, we have recently found that the GC-GR complex can upregulate the expression of bcl-X_L via a direct binding of the GR/STAT5 complex on the putative STAT5 binding site (Xu et al., 2008). Interestingly, the GR transrepression function is associated strongly with many of GCs' anti-inflammatory properties, while the GR transactivation function is associated with GC side-effects including osteoporosis and type-II (insulin resistant) diabetes (McMaster and Ray, 2007; Newton and Holden, 2007). These phenotypic changes initiated by the GC-GR genomic pathway may take hours or even longer before complete culmination. However, some of the observed anti-inflammatory and immunosuppressive effects by GCs occur faster, leading to the discovery of GC nongenomic mechanisms.

The nongenomic signaling mechanisms of GR include nonspecific interactions of GC with cellular membranes, the specific interaction of GC with membrane-bound GR and GC-GR cytoplasmic signaling (Fig. 2; Stahn et al., 2007). GCs can change biological properties of

plasma and mitochondrial membranes at high concentrations, leading to changes in lipid peroxidation and membrane permeability. GCs diminish ATP production by inhibiting oxidative phosphorylation and increasing mitochondrial proton leak. GCs' interaction with the plasma membrane also results in rapidly reduced calcium and sodium cycling across the membrane. Membrane-bound GR is thought to be a variant of the cytosolic receptor that results from differential splicing, promoter switching or posttranslational editing (Bartholome et al., 2004). Its function is best illustrated by a quick inhibition of the enzymatic activities of lymphocyte-specific protein tyrosine kinase and Fyn after a synthetic GC (dexamethasone) targeting of membrane-bound GR (Lowenberg et al., 2005; Lowenberg et al., 2006). Finally, GC-GR cytoplasmic signaling is mediated by proteins released from the GR multiprotein complex following the binding of GC to GR in the cytoplasm.

1.2. MR signaling pathways

The gene encoding the human MR (*NR3C2*) is located on chromosome 4q31.1 and has ten exons (Pippal and Fuller, 2008). MR has a structure similar to that of GR with three major functional domains: an N-terminal domain, a conserved DNA-binding domain (zinc-finger motif), and a C-terminal ligand-binding domain. The N-terminal domain of the MR protein is the longest among all the steroid receptors, containing of two distinct activation function regions (AF1a and AF1b). The MR DNA-binding domain is 94% identical with that of GR. Through this domain, MR is able to form homodimers or can heterodimerize with GR and other members of steroid receptors. The MR ligand-binding domain shows about 55% homology to other steroid receptors. It contains a ligand-dependent AF-2 region that recruits coactivators. MR, similar to GR, interacts with a large variety of proteins such as chaperone proteins and immunophilins in the cytoplasmic compartment. Upon hormone binding, MR dissociates from its protein complex, undergoes nuclear translocation and modulates gene expression by binding to the same DNA sequences (GRE) that GC-GR complex binds. However, a recent study found that DNA sequences vary extensively around GREs, which suggests a distinct set of "GRE" (perhaps better termed "MRE") for MR-regulated genes (So et al., 2007). As with GR, MR can signal through nongenomic pathways (Wehling et al., 1992). Many of these MR nongenomic pathways result from crosstalk with other signaling cascades, such as activation by Src kinase of the epidermal growth factor receptor causing subsequent downstream signaling through the MAP kinase pathway (Grossmann and Gekle, 2008). Also similar to GR, a membrane-bound MR nongenomic pathway has been reported in the hippocampus (Karst et al., 2005).

GCs mediate distinct physiological responses from MCs, which reflect in their names. At the system level, GCs help regulate glucose metabolism, along with lipid/protein metabolism, blood pressure, and immune responses, while MCs regulate electrolyte (mainly sodium) balance. Thus, one obvious question is how the selective responses between MCs and GCs are achieved. Extensive studies have revealed specificity is regulated at three levels. First, at the pre-receptor level, the most effective way to control GC and MC responses is through enzymatic inactivation of GC by 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2). Although MR binds to GCs and MCs with equivalent high affinity *in vitro*, there is an up to 1000-fold molar excess of circulating GCs *in vivo*, 11 β -HSD2 converts GCs into receptor-inactive 11-dehydrocorticosterone, enabling MC-specific activation in certain target tissues expressing this enzyme (Pippal and Fuller, 2008). Another isoform, 11 β -HSD1, mostly converts nonfunctional 11-ketoadrenocorticoids into GC when there is a high NADP level (such as in the brain), thus enhancing the signaling of GCs relative to MCs. A second method for differentiating responses is at the receptor level. GCs bind to MR, but dissociate more rapidly than MCs from the receptors (Lombes et al., 1994). Further, there is a decreased transactivation potential of the GC-MR complex compared to the MC-MR complex because of a very weak interaction between the N-terminal domain and the C-terminal ligand-binding

domain after MR binds to GCs (a strong interaction is observed after MR binds to MCs). Finally, GR expression is present in most tissues while MR expression is more restricted. In cells expressing both GR and MR without the 11 β -HSD2, such as in the hippocampus, the MR signaling pathways should be first activated by GCs because of its high affinity for GCs. Under conditions causing high GCs levels (i.e., noise exposure), An activation of GR signaling would be followed due to the excess GCs. In cells expressing both receptors and 11 β -HSD2, GCs should have effects via the MR signaling pathways only after its concentration has saturated the binding of 11 β -HSD2. Because GRs in these cells potentially never have a chance to bind GCs, their function in these cells is unknown, which illustrates our lack of complete understanding of GR pathways.

2. The role of the glucocorticoid signaling pathways in the cochlea

In the cochlea. The presence of GR and MR in the cochlea was discovered 20 years ago by *in vitro* binding assays (Rarey and Luttge, 1989). The presence of GR in the inner ear is subsequently confirmed by enzyme-linked immunosorbent assay (Rarey et al., 1993; Rarey and Curtis, 1996; ten Cate et al., 1993). Via *in situ* hybridization of the rat cochlea, GR mRNA is detected in spiral ligament cells, spiral limbus cells, and SGNs, but is absent in the stria vascularis cells and in the cells of the organ of Corti (ten Cate et al., 1993). A similar pattern is observed in the cochlea of guinea pigs with one exception - the presence of GR mRNA in the stria vascularis (Terunuma et al., 2003). Interestingly, by immunohistochemical methods, GR immunoreactivity is found in the organ of Corti beyond regions positive for the GR mRNA (ten Cate et al., 1993; Zuo et al., 1995; Shimazaki et al., 2002). In the organ of Corti, GR immunoreactivity is present in the supporting cells, but with ambiguous labeling in hair cells. Thus, the GR mRNAs and its protein products are present in spiral ligament cell, spiral limbus cells, and SGNs, but not expressed in the inner hair cells. Since GR mRNA is found in the stria vascularis of guinea pigs and GR positive immunoreactivity in the rat stria vascularis, the absence of GR mRNA detection in the rat cochlea could be due to the sensitivity of the *in situ* probe, as it is likely that GR mRNA, if expressed in the stria vascularis, is weak (Erichsen et al., 1996). The adult GR expression pattern in the cochlea is achieved by postnatal day 14 in mice (Erichsen et al., 1996), and can be regulated following acoustic stress (Tahera et al., 2006b).

The presence of MR in the cochlea was first characterized by radio-binding assays (Pitovski et al., 1993; Sinha and Pitovski, 1995). The highest level of binding is found in the stria vascularis and spiral prominence. The presence of MR mRNA is present in SGNs and marginal cells of the stria vascularis (Furuta et al., 1994). Strong MR immunoreactivity is present in the stria vascularis, spiral ligament, outer hair cells, inner hair cells, and SGNs. Moderate to weak MR staining is present in the spiral limbus (Yao and Rarey, 1996). The data discrepancy between the findings from *in situ* hybridization and immunostaining in the spiral ligament and hair cells again could be due to the sensitivity of *in situ* probes or cross-immunoreactivity of antibodies against MR. The presence of 11 β -HSD1 (based on the size of the band on the Western blot detected by the antibody used in these studies) in the rat cochlea is found mainly in the spiral ligament (ten Cate et al., 1994; ten Cate et al., 1997). It is still unknown whether 11 β -HSD2 is present in the cochlea in spite of its key role in deactivating GCs.

Although no studies have been designed to directly examine the presence of GC genomic and nongenomic signaling pathways in the inner ear, several reports have clearly demonstrated their existence in the cochlea (Canlon et al., 2007; Lee and Marcus, 2002; Trune et al., 2007). The presence of these GC signaling components in the cochlea suggests potentially important roles of GC signaling pathways in physiological and pathological responses of the inner ear to acute increases of GCs such as in noise-induced hearing loss (NIHL), or to chronic excess GCs such as in age-related hearing loss (presbycusis).

2.1. The role of GCs in NIHL

In response to acute stressful stimuli such as noise exposure, a temporary increase of GC release likely mediates adaptive responses to restore physiological and behavioral homeostasis. Although it is one of the most common occupational diseases, NIHL in humans has resisted detailed mechanistic studies because of mixed pathology and incomplete noise history. Thus, various animal models have been developed to study cellular and molecular mechanisms underlying NIHL. Inbred mouse models are particularly useful because of minimal variance within strains and availability of genetic manipulations (Ohlemiller, 2006; Tian et al., 2006). Through these models, ample evidence exists for a protective role of GCs against NIHL.

Extensive studies in various animals have produced a mostly consistent picture of noise-induced injuries in the cochlea (Nordmann et al., 2000; Ohlemiller, 2006; Wang et al., 2002). Functionally, there are two typical phases of hearing loss after noise exposure: temporary threshold shift (TTS) that is prominent within the first 24 hours, and permanent threshold shift (PTS) two or three weeks after exposure (Clark, 1991; Nordmann et al., 2000; Quaranta et al., 1998). The extent of damage in both TTS and PTS are based on noise intensity (Wang et al., 2002). Recently, Kujawa and Liberman (2006) found an extensive delayed loss of SGNs in noised exposed mice, even in the group showing no damages in their hearing thresholds two weeks after the noise exposure. Degeneration of afferent fibers in the organ of Corti during NIHL was also clearly observed in other animal models (Lawner et al., 1997; Saunders et al., 1991; Slepecky, 1986).

Synthetic GCs such as methylprednisolone are widely used for clinical therapy of neural trauma such as spinal cord injury. In studies that mechanically damaged the cochlear nerve, analogous to spinal cord trauma, it has been shown that methylprednisolone improved neuron survivability (Sekiya et al., 2001). Synthetic GCs are also used clinically to treat hearing loss in a variety of cochlear disorders such as autoimmune inner ear disease, tinnitus and Menière's disease (Dodson and Sismanis, 2004; Dodson et al., 2004; McCabe, 1979). Although no current reports were found on the clinical use of synthetic GCs for acoustic trauma, stress events before the noise exposure such as restraint stress, sound preconditioning (exposure to lower intensity noise prior to higher intensity noise that causes damage) or heat exposure, have been found to be protective against NIHL in animal models (Paz et al., 2004; Wang and Liberman, 2002; Yoshida et al., 1999). Subsequent studies have suggested that this protection against NIHL is due to the activation of GR signaling pathways, particularly, via the GR/NF- κ B pathway (Canlon et al., 2007; Tahera et al., 2006b; Tahera et al., 2006c). In addition, synthetic GCs such as dexamethasone and methylprednisolone can also protect against NIHL (Canlon et al., 2007; Henry, 1992; Lamm and Arnold, 1998; Sendowski et al., 2006; Tabuchi et al., 2006; Tahera et al., 2006b; Tahera et al., 2006c; Takahashi et al., 1996; Takemura et al., 2004), consistent with GCs' biological role of promoting neuronal adaptation and survival (McEwen, 2008). Interestingly, MR antagonists have no effects on NIHL (Tahera et al., 2006a).

Damage to SGNs, such as massive swelling of afferent dendrites under IHCs, is found following noise exposure (Lang et al., 2006; Le Prell et al., 2004; Puel et al., 1998; Robertson, 1983). While previous studies suggest protection of hair cells by GCs (particularly OHCs) after noise exposure (Hirose et al., 2007; Sendowski et al., 2006; Takahashi et al., 1996; Takemura et al., 2004), no direct data at the cellular level is available for demonstrating GC effects on SGNs after noise exposure. One study found a significantly smaller shift in the threshold of compound action potentials in albino guinea pigs after they were treated with methylprednisolone before exposure noise, implying a possible protective effect on SGNs (Takahashi et al., 1996). In contrast, at the molecular level, the role of GR genomic signaling pathways during NIHL has been clearly delineated in SGNs (Tahera et al., 2006b; Tahera et al., 2006c). A decrease of GR mRNA is found after noise exposure in SGNs, resulting in reduced nuclear translocation of GR and increased NF- κ B activity in SGNs. Notably, an

opposite pattern is observed when the GR signaling pathways are blocked by the combination treatment of a GC synthesis inhibitor and a GR antagonist, correlating with worsening NIHL. NF- κ B appears to have a protective role in NIHL, as mice lacking the p50 subunit of NF- κ B are more susceptible to NIHL (Lang et al., 2006). In these same mice, an accelerated age-related loss of SGNs is observed as well. Modulations of other signaling systems by GCs may also be involved in GC protective effects against NIHL. Enhanced biosynthesis of glutathione in SGNs by dexamethasone can contribute to this protective effect (Nagashima and Ogita, 2006). GC protective effects could also be due to direct or indirect modulations of MAP kinases (Canlon et al., 2007) and calcium channels (Le Prell et al., 2007), but further studies are needed to explore these possible interactions.

2.2. The role of GCs in presbycusis

Although the short-term activation of GC signaling pathways has protective effects against NIHL, its effects on presbycusis is unknown. In the central nervous system, the long-term activation of GR signaling is clearly detrimental to neurons (McEwen et al., 1992). During aging, a chronic increase of GCs occurs due to the deregulation of the HPA axis. In the brain, this increase contributes to age-related functional declines such as age-related loss of memory (Joels et al., 2004; McEwen et al., 1992; McEwen, 2005; McEwen, 2008; Sandi and Pinelo-Nava, 2007). Most studies in this area focused on the hippocampus, a neural structure important for learning and memory, and three main findings are reported: (1) atrophy of neuronal processes such as CA3 apical dendrites; (2) inhibition of adult neurogenesis at the dentate gyrus; and (3) decreased ability of hippocampal neurons to survive further insults. Excessive GCs also kill hippocampal neurons although this finding has been questioned with the emergence of unbiased stereology for counting neurons. The potential loss of hippocampal neurons due to prolonged exposure to increased GCs raises the possibility of age-related elevated GCs contributing to SGN loss.

Previous studies of presbycusis in human and animal cochleae found mixed pathology in the organ of Corti, SGNs, and lateral wall (Adams and Schulte, 1997; Bohne et al., 1990; Covell and Rogers, 1957; Schuknecht, 1964; Schuknecht and Gacek, 1993; Shimada et al., 1998). Based on observations of human temporal bones, four types of presbycusis are proposed by Schuknecht and Gacek (1993): (1) sensory (hair cell loss), (2) neural (SGN loss), (3) strial (atrophy of the stria vascularis), and (4) cochlear conductive (stiffening of the basilar membrane). One important implication of this classification is that these structures could degenerate independently during aging. Therefore, one question addressed in previous studies is whether age-related loss of hair cells and SGNs are linked. After chemical or mechanical damage of hair cells, SGNs are rapidly lost, which is consistent with findings of trophic support of SGNs by hair cells (Ernfors et al., 1995; Fritzsche et al., 1997; Hossain et al., 2006; Takeno et al., 1998). However, loss of SGNs without associated loss of hair cells is common during aging (Keithley and Feldman, 1979; Keithley et al., 1989; Ryals and Westbrook, 1988; Suzuka and Schuknecht, 1988; White et al., 2000). Thus, age-related loss of SGNs (neural presbycusis) may be independent of loss of hair cells due to unknown mechanisms.

To date, no direct evidence has linked the excess of GCs during aging to neural presbycusis although high levels of MCs (aldosterone) in human serum is found to correlate with better hearing during aging (Tadros et al., 2005). It has been found previously that an accelerated loss of SGNs occurs during aging in mice lacking the β 2 nAChR subunit (Bao et al., 2005), and an accelerated age-related increase of GCs has been described in these mice (Zoli et al., 1999). Recently, a similar observation of accelerated age-related SGN loss was made in mice lacking NF κ B, which have been shown to have increased SGN nuclear translocation associated with increased GCs in the cochlea (Lang et al., 2006; Tahera et al., 2006b). This indirect evidence suggests a role of excessive GCs in age-related loss of SGNs.

3. Available pharmacological and genetic tools

The identification of the potent anti-inflammatory activities of GCs has led to their wide use in treating a great variety of allergic and inflammatory diseases (Hench et al., 1950). Serious side effects induced by these drugs quickly become obvious and methods to limit unwanted effects are sought (McMaster and Ray, 2008). To reduce side effects, synthetic GCs are developed in several phases. In the early phase, the aim is to eliminate MC effects. For example, a C1-C2 double bond in the A-ring of cortisol is introduced to generate prednisolone. Introduction of a 16 α -hydroxyl or 16 α -methyl group reduces sodium and water retention. Dexamethasone combined 1-dehydrogenation with 16 α -methylation and 9 α -fluorination can increase resistance to metabolic degradation, and is a highly potent and selective GR agonist. In the second phase, various modified GCs are developed for specific tissue targets such as skin and lung to avoid GC systemic side-effects (Jacob and Steele, 2006; Uings and Farrow, 2005). Since GRs' transrepression function is sufficient in mediating GCs' anti-inflammatory properties, recent research to selectively avoid GR's transactivation function has been undertaken (Newton and Holden, 2007). With this extensive research effort, numerous synthetic GC drugs are now clinically available (see Table 1 showing commonly used glucocorticoids used systemically and their relative potencies), which can be classified based on their structure modifications, or on their potency (Jacob and Steele, 2006). All of these drugs are GR agonists; however, some of them can also activate MRs with fludrocortisone a potent MR agonist.

Glucocorticoids are delivered either systemically or intratympanically to the inner ear for treatment. Early clinical applications only used systemic administration of glucocorticoids (McCabe, 1979; Wilson et al., 1980). Subsequently it has been shown that inner ear concentrations of glucocorticoids are higher in both endolymph and perilymph following intratympanic application, which relies on absorption through the round window (Parnes et al., 1999). Through modeling and direct measurement of drug levels, a concentration gradient of glucocorticoids forms after intratympanic administration with highest levels existing at the base (Plontke et al., 2007; Plontke et al., 2008). Further, one study has shown that following intratympanic placement of dexamethasone, the active drug is immunohistochemically located in many areas of the inner ear, including strong labeling in the spiral ganglion (Hargunani et al., 2006). This large array of drugs and different methods of delivery provides powerful pharmacological tools, allowing researchers to selectively dissect GC and MC signaling pathways in the inner ear.

Genetic manipulation provides a complementary to pharmacological agents in understanding glucocorticoid pathways. Various recently developed transgenic models, particularly in mice, are providing new insights into GC signaling pathways (Erdmann et al., 2008; Kolber et al., 2008). Mice without functional GR die shortly after birth (Cole et al., 1995). MR^{-/-} mice undergo normal prenatal development, but die during the second week after birth following symptoms of pseudoaldosteronism (Berger et al., 1998). As the auditory system is established at least two weeks after birth, these transgenic mouse models are not useful for dissecting GC signaling in the inner ear. Fortunately, the Cre-loxP recombination system can ablate GR or MR in selected cell populations when the loxP-flanked gene functions normally, but can be deleted in cells expressing Cre recombinase. The GR^{loxP} and MR^{loxP} mouse models have been utilized to uncover the function of GR and MR in specific organs such as in the liver and hippocampus (Berger et al., 2006; Erdmann et al., 2008; Kolber et al., 2008). To date, these models have not been used to study GC signaling in the cochlea. However, with the recently created transgenic mouse models expressing Cre recombinase specifically in SGNs (Raft et al., 2007; Tian et al., 2006; Yu and Zuo, 2009), the time to study the role of GC signaling pathways in SGNs during aging and NIHL may have finally arrived.

Summary

The GC signaling system has evolved for the maintenance of homeostasis after acute stress. In the inner ear, the GC signaling pathways are present in various cells, although a detailed expression pattern for some key factors is still missing. For acute acoustic trauma such as NIHL, GCs clearly have protective effects via the GR signaling pathways, but further studies are needed to identify the exact GR pathways. For age-related hearing loss, little is known whether GCs contribute to age-related loss of auditory neurons, particularly SGNs, although extensive evidence exists for the detrimental effects of GCs on neurons in the brain during aging. Therefore, it is important to take advantage of current molecular and pharmacological tools to dissect the role of GC signaling in hearing loss.

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Fig. 1.

Genomic pathways of GC signaling pathways. Binding of GC to GR or MR leads to the release of immunophilins, co-chaperones, heat shock proteins (HSP), and the mitogen-activated protein kinases (MAPK). The GR-GC, GR-MR-GC, or MR-GC complex moves into the nuclei and regulates gene expression by binding to glucocorticoid response elements (GREs) or the same elements with conserved adjacent sequences preferring the MR-GC complex ("MREs"). These complexes can also regulate gene expression by interactions with other transcriptional factors (TF).

Fig. 2.

Nongenomic pathways of GC signaling pathways. Besides acting at the genomic level, GC can influence cells by directly acting on the cellular membrane, mitochondrial, and membrane-bound GR or MR. After GC binds to GR or MR in the cytoplasm, other proteins released from the receptor complex can also influence cellular signaling networks.

Table 1

Commonly used systemic glucocorticoids as therapeutic agents.

CORTICOSTEROIDS	Equivalent dose (mg)	Relative anti-inflammatory potency	Relative mineralocorticoid potency	Half-life (hr)
betamethasone	0.6-0.75	20-30	0	36-54
cortisone	25	0.8	2	8-12
dexamethasone	0.75	20	0	36-54
fludrocortisone	-	10	125	18-36
hydrocortisone	20	1	2	8-12
methylprednisolone	4	5	0	18-36
prednisolone	5	4	1	18-36
prednisone	5	4	1	18-36
triamcinolone	4	5	0	12-36