Corticosteroid Therapy for Hearing and Balance Disorders

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ABSTRACT

This review addresses the current status of steroid therapies for hearing and vestibular disorders and how certain misconceptions may be undermining the efficacy in restoring normal ear function, both experimentally and clinically. Specific misconceptions addressed are that steroid therapy is not effective, steroid-responsive hearing loss proves an underlying inflammatory problem in the ear, and steroids only have application to the hearing disorders listed below. Glucocorticoid therapy for hearing and balance disorders has been employed for over 60 years. It is recommended in cases of sudden hearing loss, Menière’s disease, immune-mediated hearing loss, and any vestibular dysfunction suspected of having an inflammatory etiology. The predominant steroids employed today are dexamethasone, prednisone, prednisolone, and methylprednisolone. Despite years of use, little is known of the steroid responsive mechanisms in the ear that are influenced by glucocorticoid therapy. Furthermore, meta-analyses and clinical study reviews occasionally question whether steroids offer any benefit at all. Foremost in the minds of clinicians is the immune suppression and anti-inflammatory functions of steroids because of their efficacy for autoimmune hearing loss. However, glucocorticoids have a strong binding affinity for the mineralocorticoid (aldosterone) and glucocorticoid receptors, both of which are prominent in the ear. Because the auditory and vestibular end organs require tightly regulated endolymph and perilymph fluids, this ion homeostasis role of the mineralocorticoid receptor cannot be overlooked in both normal and pathologic functions of the ear. The function of the glucocorticoid receptor is to provide anti-inflammatory and antiapoptotic signals by mediating survival factors. Anat Rec, 295:1928–1943, 2012. ©2012 Wiley Periodicals, Inc.

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CORTICOSTEROIDS

Steroid hormones produced by the adrenal cortex are called corticosteroids. These include the glucocorticoid cortisol (corticosterone) and the mineralocorticoid aldosterone. The two corticosteroid receptors expressed in the inner ear are the glucocorticoid receptor and the mineralocorticoid receptor. The affinity of the mineralocorticoid receptor is higher than the glucocorticoid receptor (de Kloet and Reul, 1987), indicating that at basal levels the mineralocorticoid receptor is maximally activated while the glucocorticoid receptor is maximally activated after a stressor. Both the mineralocorticoid and glucocorticoid receptors are ligand-driven transcription factors that differ in their downstream signaling mechanisms. The glucocorticoid cortisol has a number of

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functions, including immune suppression and carbohydrate, lipid, and protein metabolism. Aldosterone is involved primarily with Na\(^+\) and K\(^+\) transport, figures prominently in kidney clearance and resorption of these ions, and is critical for ion homeostasis throughout the body. Circulating levels of glucocorticoids are \(~1,000\) fold higher than the mineralocorticoid aldosterone (Schimmer and Parker, 2006).

The HPA Axis

The hypothalamic-pituitary adrenal axis (HPA) is a neuroendocrine system that mediates responses to stress and where the steroid hormone cortisol plays a major role (Fig. 1). The paraventricular nucleus of the hypothalamus coordinates stressful signals from the limbic system, brain stem and other brain regions by activating different genes, including corticotropin-releasing hormone (CRH) and arginine vasopressin. The activation of these peptides causes the release of adrenocorticotropic hormone (ACTH) from anterior pituitary which, in turn activates the synthesis and secretion of glucocorticoids from the adrenal glands. Cortisol is the predominant glucocorticoid in humans whereas corticosterone dominates in rodents. The concentration of corticosterone in the blood has a specific pattern depending of the species and diurnal activity. In rodents the peak of the corticosterone concentration is at night time while for humans it is the first half of the day (Buijs et al., 2003; Walker et al., 2010). When circulating in the blood, corticosterone is bound to a corticosteroid binding globulin which controls the diffusion of corticosterone through the cell membrane (Henley and Lightman, 2011). Upon release from the globulin, corticosterone can diffuse into the cytoplasm. Once corticosterone enters the cytoplasm, there is an additional control mechanism that is mediated by 11β-hydroxysteroid dehydrogenase (11β-HSD). This enzyme is involved in the conversion of 11-deoxycortisol to cortisol in the adrenal cortex. This 11β-HSD is one of the regulators of glucocorticoids accessibility to the glucocorticoid receptor, and its mRNA synthesis in the cochlea is upregulated by dexamethasone (Kim et al., 2009). One function of 11β-HSD is to control the availability of corticosterone so as to not activate the high-affinity mineralocorticoid receptor, thereby allowing its access for the glucocorticoid receptor (Seckl and Meaney, 2004; Walker and Andrew, 2006).

**Glucocorticoid Receptor Signaling**

The glucocorticoid receptor is a member of the nuclear receptor protein family and consists of an N-terminal transactivation domain, a central DNA binding domain and a C-terminal domain. The N-terminal domain contains the transcriptional activation function (AF-1) that also binds co-regulators. The central DNA binding domain is a conserved region and contains the glucocorticoid-responsive elements that bind target DNA sequences (Gross et al., 2009). The \(\alpha\)-isoform of the glucocorticoid receptor is the most studied and it is sequestered in the cytoplasm with a heat shock protein 90 (hsp90)-chaperone complex (Hutchison et al., 1993). When glucocorticoids bind to the receptor, a conformational change occurs and allows release from the hsp90 complex. As a consequence, the receptor translocates to the nucleus and binds to specific DNA sequences, the glucocorticoid response element. Glucocorticoid receptors can also interact with other transcription factors, such as activator protein-1 (AP-1), CCAAT enhancer binding protein (C/EBP), and nuclear factor-1 (NF-1), or by direct protein–protein interaction, which does not require the DNA binding itself (Kassel and Herrlich, 2007; Johansson-Haque et al., 2008). Both mineralocorticoid and glucocorticoid receptors bind to glucocorticoid response elements, but only the glucocorticoid receptor is capable of interacting with transcription factors, such as activating protein (AP-1) and NF-xB. NF-xB is modulated by acoustic trauma or by restraint stress and its expression was found to modulate auditory sensitivity (Tahera et al., 2006a,b). These findings provide mechanisms that explain how glucocorticoids block primary stress reactions by a blockade of the interaction of the glucocorticoid receptor monomers with transcription factors and co-regulators.

Glucocorticoid receptors are dynamic and are continuously being either upregulated or downregulated depending on the overall stress hormone levels in the body. Endogenous glucocorticoids are hormones released following stress-related events, such as acoustic trauma, and function to maintain homeostasis (Canlon et al., 2007). Stress is a process of increased arousal with the primary biological function of maintaining homeostasis. Behaviorally, it aims to mobilize energy to increase survival through fight–flight reactions. Short-term stress with sufficient recovery is generally beneficial, whereas long-term stress exposure without sufficient recovery may lead to various detrimental health effects. Short-term stress exposure (e.g., physical exercise) increases the secretion of stress hormones (e.g., cortisol) and anabolic hormones (e.g., dehydroepiandrosterone, testosterone, estrogen). Following the termination of stress, recovery-related responses and anabolism are increased. Consequently, the short-term stress reaction is adaptive and may have several beneficial health effects. However,
without sufficient restitution, recovery-related functions, such as activation of parasympathetic system and secretion of anabolic hormones, are disturbed. It is thus imperative to have background information about the individual's stress levels before administering glucocorticoid therapy. Glucocorticoid therapy will affect those individuals with higher cortisol values differently than individuals with low cortisol values.

**Glucocorticoid Therapy Effects on the HPA Axis**

The addition of exogenous glucocorticoids by glucocorticoid therapy will affect the balance of the HPA axis. Because of numerous glucocorticoid-driven cellular functions, supplementing natural levels with therapeutic glucocorticoids (prednisone, prednisolone, dexamethasone) for immune suppression can lead to the severe side effects of fluid and electrolyte imbalance, hypotension, hyperglycemia, susceptibility to infection, osteoporosis, myopathy, behavioral disturbances, cataracts, fat redistribution, etc. (Nadel, 1996; Schimmer and Parker, 2006; Alexander et al., 2009; Smets et al., 2010). The synthesis and secretion of the glucocorticoids is tightly controlled by negative feedback mechanisms (Fig. 1). The negative feedback mechanism is an effective feature of hormone secretion and is tightly regulated by the hypothalamus and the pituitary gland. The negative feedback system results in hormonal homeostasis by reducing brain CRH secretion, resulting in a reduction of pituitary ACTH release that will reduce adrenal corticosterone secretion into the blood stream (Herman and Cullinan, 1997).

Both glucocorticoids and mineralocorticoids are susceptible to negative feedback and their natural production is lowered if serum levels rise due to supraphysiological therapeutic steroids. Even a small amount of supplemental glucocorticoid in ear drops is enough to decrease natural cortisol production to a fraction of normal (Abraham et al., 2005), with some patients requiring a year to restore natural levels (Schimmer and Parker, 2006). This has implications for hearing and balance disorders since therapeutic doses may substantially reduce serum levels long term. Control of these side effects is part of the rationale for giving steroids transtympanically (Rauch et al., 2011; Vlastarakos et al., in press; Stachler et al., 2012).

**HISTORY OF STEROID TREATMENTS FOR EAR DISORDERS**

Corticosteroid treatments have become the standard therapy for many forms of hearing loss, such as autoimmune inner ear disease, sudden hearing loss, and Menière's disease. Cogan (1945) described the association of auditory and vestibular dysfunction with eye disease and established the inflammatory link between the inner ear and systemic autoimmune diseases. A few years later Hilger and Goltz (1951) treated a person with supposed inflammation in the ear with corticosteroids and proposed such a therapy be included in the armamentarium of inner ear treatments. Glucocorticoid therapy for autoimmune related ear disorders was employed during the 1950s and 1960s with some success (Peitersen and Carlson, 1966; Smith, 1970; Stephens et al., 1982). Also in the 1960s Addison's disease (adrenal cortical insufficiency) patients were treated with a variety of glucocorticoids and mineralocorticoids with positive results on hearing and balance (Henkin and Daly, 1968). McCabe coined the term autoimmune sensorineural hearing loss and recommended the use of steroids and cyclophosphamide to suppress the immune response (McCabe, 1979). The anti-inflammatory and immune suppressive function of glucocorticoids (Flammer and Rogatsky, 2011) led to their common use for hearing and vestibular disorders suspected of being due to inner ear inflammation. The more accepted term today is immune mediated inner ear disease because the reversibility of such hearing loss precludes it being due to sensorineural damage.

Despite the use of steroids for ear disorders in the past 60 years, there is limited understanding of their role in reversal of hearing and vestibular dysfunction. Although glucocorticoids have numerous functions, their immune suppressive role was often credited for their positive results. With such a background, glucocorticoids have become the main treatment for inner ear disorders. However, other cellular functions besides immune suppression may underlie their positive results. Glucocorticoids have a strong binding affinity for the mineralocorticoid receptor, so the cellular and molecular mechanisms in the ear under their control are still largely undetermined. Thus, it is not always clear what steroids are doing in the ear because it is not clear what is wrong with the ear in the first place in steroid-responsive hearing loss. Working under the common assumption that their only role is immune suppression, little effort has been made to clarify the exact metabolic processes in the ear that are under their control. Often this is the only therapy attempted, despite a greater understanding today of inner ear biology and its numerous processes driven by other steroid hormones (Qvortrup et al., 1996; Sawada et al., 1997; Guimaraes et al., 2006; Price et al., 2009; Andrews and Honrubia, 2010; Trune and Kempton, 2010). This is in part due to a number of misconceptions about steroid driven functions in the ear and how these relate to steroid responsive hearing and vestibular problems.

It is our goal in this review to evaluate the latest relevant research in the field to provide a better understanding of steroid driven molecular processes in the normal ear, how these processes may be at risk in various forms of hearing loss, and why steroid treatments may or may not be effective. It is not our goal to provide an exhaustive literature review of all the research in which steroids have been applied to the ear. That can be achieved by the reader in just a few moments on Medline or PubMed. Instead, we will focus on misconceptions regarding steroid-responsive and nonresponsive hearing loss and recent key studies so that the reader can better understand their relevance for the treatment of hearing loss. Gaps in our understanding will be addressed in suggested studies.
MISCONCEPTIONS ABOUT CORTICOSTEROID THERAPY FOR HEARING AND VESTIBULAR DISORDERS

Steroids have No Positive Impact on the Hearing and Vestibular Dysfunction

Despite numerous clinical reports of the success of steroid treatments for hearing and vestibular disorders, occasionally large reviews provide statistical evidence that such treatments did not lead to measurable improvement (Byl, 1984; Wei et al., 2006; Conlin and Barnes, 2007a,b; Nosrati-Zarenoe et al., 2007; Stachler et al., 2012). The spontaneous rate of recovery in sudden hearing loss ranges from 30 to 60% (Mattox and Simmons, 1977), which complicates conclusions about steroid efficacy. Furthermore, the use of intratympanic steroids as primary or salvage treatments also is occasionally questioned (Lamm and Arnold, 1999; Doyle et al., 2004; Piccirillo, 2011), although recent large analyses provide evidence that this delivery method is as effective as systemic delivery (Rauch et al., 2011; Seggas et al., 2011; Spear and Schwartz, 2011; Vlastarakos et al., in press; Stachler et al., 2012). Many small studies conclude steroids are helpful in many cases, but there is always a number of patients who are not helped (Garduno-Anaya et al., 2005; Haynes et al., 2007; Chen et al., 2010; Raymundo et al., 2010; Kakehata et al., 2011; Li et al., 2011). Many of these studies were intratympanic salvage therapies after failure of systemic delivery, so these are people who had spontaneously recovered. However, even with intratympanic therapy, considerable variation is seen in drug used, doses, injection frequency and amount, delivery method, and criteria used for improvement (Raymundo et al., 2010; Seggas et al., 2011; Vlastarakos et al., in press; Stachler et al., 2012).

So the question remains, do steroids improve one’s chances for hearing and vestibular recovery compared no treatment? One might argue that no hearing improvement in some does not negate to measurable improvement in others. Also, if there are multiple hormonal and molecular mechanisms required for normal ear function, why would one expect a single therapy to reverse all hearing and vestibular deficits? While everyone wants medical magic, it seems a bit naïve to think a “one-therapy protocol” would cure all inner ear problems. Given the molecular complexity of the ear and the multiple underlying pathologies proposed in sudden hearing loss, immune-mediated hearing loss, Menière’s disease, etc., it is simply not logical to expect a single therapeutic approach to reverse every hearing and vestibular defect (Mattox, 1980). Also, a recent power analysis of sudden hearing loss treatment suggested that a study would have to include 1,000 patients to show a statistically significant improvement of 10% more people over spontaneous recovery (Wei et al., 2006). Thus, it appears to be as much a problem with statistics as it is steroids. This becomes even more critical in current efforts to establish evidence-based medicine guidelines for treatment of hearing and vestibular disorders (Shin et al., 2010, 2011; Stachler et al., 2012). If treatments outcomes are a factor in developing patient therapy protocols, and no evidence of efficacy can be demonstrated, then patient treatment cannot be justified.

There are a number of factors that complicate the analysis of steroid efficacy, most outside the control of the treating physician or clinical researcher. These include small sample sizes, multiple underlying causes of hearing loss and vertigo, some of which are not responsive to glucocorticoids, other hormone driven ear problems, spontaneous recovery in some patients, absolutely no chance of recovery in others, time to treatment, extent of hearing loss, etc. As a result, steroid treatments are attempted with little or no insight into their potential for effectiveness. What is worse, failure of steroid therapy seldom leads to an alternative therapeutic approach. For example, would the patients not responding to glucocorticoids show improvement with diuretics, and vice versa? Thus, these are issues that impact the outcomes of treatment and impact statistical analyses.

No knowledge of thresholds before hearing loss.

There is generally no knowledge of a patient’s hearing function prior to the sudden hearing loss (Stachler et al., 2012) or Menière’s attack. Proper statistical design and analysis requires treatment group assignments to be comparable populations, but information required for that is not known. So how do you assign patients to a treatment arm? This also makes it difficult to assess degree of recovery. Is 20 dB or 50 dB PTA recovery appropriate to judge whether it was a full or partial return of function? While a 10 dB recovery may be statistically significant, is it functionally significant? If there is no measurable threshold recovery, but a 20% speech discrimination recovery, is this person improved? If a patient says their vertigo attacks are about the same frequency, but appear less severe, were the steroids effective or not? Statistical analysis requires quantification of some function, but the connection between a functional measure and steroid efficacy is often very difficult when each person has a different starting point.

No knowledge of actual cochlear or vestibular pathology.

Etiologies are varied and overlapping among hearing and vestibular disorders and there are undoubtedly multiple causes of sudden hearing loss and Menière’s disease. Those most often discussed are vascular, immune-mediated, viral, membrane rupture, trauma, and ototoxic drugs, with potential overlap even among these. However, these are not established prior to treatment, which further complicates statistical assessments of steroid efficacy. Some pathology simply may not be responsive to steroids for the hearing or vestibular dysfunction. There is virtually no accounting for cause when clinical treatments are assigned, further complicating statistical analyses of outcomes. Serum assessments are seldom done, so even heterogeneity of inflammatory markers is another potentially confounding factor. Until underlying inner ear pathology is assessed and accounted for in statistical design and analyses, steroid treatment outcomes will be inconsistent and inconclusive.

Is the steroid given targeted to the underlying problem?

There are a number of potential ear pathologies that may not be corrected by glucocorticoid treatment.
A recent review of ion homeostasis disorders in the ear showed many channels and transporters are under the control of steroids other than glucocorticoids, suggesting that their dysfunction may not be effectively remedied by a glucocorticoid therapy (Trune, 2010). These include the mineralocorticoid aldosterone, the diuretics and anti-diuretics (vasopressin), sex hormones, thyroid, insulin, etc. (Kovtrop et al., 1996; Sawada et al., 1997; Brenner et al., 2004; Coulomner et al., 2006; Guimaraes et al., 2006; Price et al., 2009; Andrews and Honrubia, 2010; Nakagawa et al., 2010; Trune, 2010). Some of these will induce hydrops in a normal animal (Salt and Plontke, 2010), indicating the sensitivity of ear homeostasis to changes in these hormones. Thus, a hearing disorder due to disruption of one of these other steroid driven processes probably would not respond to glucocorticoids and thus affect outcomes. Proof of efficacy of diuretics for Menière’s disease suffers from the same statistical design problems (Claes and van de Heyning, 2000; Thirlwall and Kundu, 2006), so how does one decide whether to give glucocorticoids versus diuretics when it isn’t determined which molecular pathway is involved. This issue is partially settled by recent clinical studies showing greater efficacy when glucocorticoids were combined with diuretics (Morita et al., 2010), antioxidants (Ahn et al., 2010). Animal studies also have shown the glucocorticoid prednisolone combined with the mineralocorticoid aldosterone was effective in preventing autoimmune hearing loss at dosage levels that were ineffective when used individually (Trune and Kempton, 2010). In light of the fact there is a critical window of days to weeks to reverse hearing loss; one may not have the time to sequentially try multiple therapies. Thus, a drug combination approach of known, but inconsistently effective, drugs or steroids may prove to be more successful for many hearing and vestibular disorders.

No assessment of underlying genetic problems.

We often think of the steroid responsive forms of hearing loss as being spontaneous or induced by some sudden metabolic, vascular, or inflammatory event. However, recent studies have shown that some forms of sudden hearing loss and Menière’s disease are correlated with gene alterations. If these defects precipitate the manifestation of hearing or vestibular symptoms, they may be less likely to respond to steroids. However, seldom is any genetic testing done for these disorders because of time and cost. Menière’s disease has long been suspected of having a familial inheritance (Paparella and Djallilian, 2002; Vrabec, 2010) and has now been correlated with alterations in genes for aquaporins (Ichiyama et al., 2010; Mallur, 2010), ouabain (Leggi et al., 2010), vasopressin and receptors (Kitahara et al., 2008; Kitahara et al., 2009), and the cytokine interleukin-1β (Furuta et al., 2011). The latter defect is also seen in hearing loss (Furuta et al., 2011). Interestingly, defects in expression of interleukin-1β and its receptor are correlated with steroid-responsive autoimmune hearing loss (Vambutas et al., 2009; Pathak et al., 2011). Sudden hearing loss is often the first symptom of an underlying autoimmune disease that manifests systemically later (Ottaviani et al., 1999; Cadoni et al., 2002; Garcia-Berrocal et al., 2003; Agrup, 2008; Amor Dorado et al., 2009; Deroee et al., 2009; Hervier et al., 2010). Also, sudden hearing loss has been correlated with inner ear anomalies of semicircular canal hypoplasia and enlarged internal auditory canals (Sugiura et al., 2005), as well as reduced size of anterior inferior cerebellar arteries that serve the affected inner ear (Psillas et al., 2005). None of these underlying genetic influences are known during treatment and subsequent statistical analyses of steroid efficacy. It is interesting to speculate that Rauch’s description of the Menière’s patient as one who represents that phenotype of a fragile ear with defective homeostatic mechanisms may actually have a genotypic basis (Rauch, 2010). Thus, the actual cause of hearing loss or vertigo may be a genetic malformation that is not fully compensated with a steroid treatment. As the unknown cause issue above, assignment to treatment arms and segregation for statistical analysis is not done for these patients, further complicating assessment of steroid efficacy.

Starting treatment too late.

Several clinical trials have shown that little recovery can be expected if the patient treatment begins more than 4–5 weeks after hearing loss onset (Mattox and Simmons, 1977; Haynes et al., 2007; Nosrati-Zarenoe et al., 2007; Rauch, 2008; Chen et al., 2010; Raymundo et al., 2010; Vlastarakos et al., in press; Stachler et al., 2012). Seldom is this time to treatment factored in a statistical analysis of outcomes. When salvage treatments with intratympanic steroids are attempted, often they are not begun until a prolonged systemic steroid treatment was attempted. When such intratympanic salvage studies take time into account, recovery of hearing in patients appears to be more likely. It is tempting to speculate why time is a factor. If the inner ear pathology of sudden hearing loss is vascular, immune-mediated, or a disrupted endolymph production, the resultant ion imbalance and loss of the endocochlear potential (EP) will create an environment that is toxic to hair cells. Mild hearing loss (EP only) will recover with stria vascularis regeneration, either spontaneously or steroid driven. However, the longer it takes to restore the proper ionic environment places the hair cell at greater risk and the worse hearing patients (EP and hair cell loss) simply cannot adequately recover the tissue damage. Even the instantaneous mixing of endolymph and perilymph during a Menière’s attack is detrimental to auditory and vestibular hair cell function, hopefully only temporarily. But the repeated insult of numerous Menière’s attacks eventually drives the fragile ear to the dead ear (Rauch, 2010) because it can no longer compensate and heal sufficiently to restore function.

Many of these confounding factors above that increase subject variance and reduce statistical significance are beyond the control and knowledge of the physicians. Furthermore, many of these factors simply cannot be determined even if the treatment grouping and outcomes tried to take them into account. Given the variance in patients and causes in many glucocorticoid treatment studies, it is remarkable steroids show such consistently positive results as they do. Thus, it is our assertion that steroids are effective in treating hearing and vestibular dysfunction. However, if we knew more about the underlying pathology in many patients, the outcomes could be
even better by targeting therapies that better matched the patient’s condition. Those that do not respond to steroids may be candidates for an alternative therapy (vasodilators, diuretics, antioxidants).

Studies needed.

(a) Better diagnostic protocols are needed to clarify the underlying problem in patient hearing loss. Any improvement in defining and segregating patients on the basis of pathology will improve statistical reliability of treatment outcomes. This also will help differentiate those patients that should benefit from glucocorticoids versus some other therapy. This can be accomplished by a number of existing methods, such as serum assessments (Dornhoffer et al., 1997; Amor Dorado et al., 2009), genetic screening (Shearer et al., 2010), etc.

(b) Advancements in imaging techniques now make it possible to identify hydrops and possibly even vascular leakage in the ear (Naganawa et al., 2002; Sugiura et al., 2006; Yoshida et al., 2008; Pyykkö et al., 2010; Suzuki et al., 2011). If this information was available to the physician in developing the treatment protocol, it would help target the treatment to the disease process. This also could be assessed after effective or noneffective treatments to better correlate treatments and outcomes.

(c) Some efforts have been made to develop predictive models for steroid treatments (Suzuki et al., 2011a), particularly time to treatment and degree of hearing loss. Expanding the number of factors employed may better differentiate the most relevant predictive measures. This also needs to be done for different steroids, including nonglucocorticoids.

(d) Combination therapies need to be developed to capture more than just glucocorticoid responsive patients. Clinical treatments must be rethought to include the numerous other steroid and hormone driven processes in the ear that might be at risk in some forms of hearing loss. Defects in some of these other hormones can be assessed by serum to develop a better targeted therapy for each patient, which is the goal of evidence-based medicine (Shin et al., 2010; Shin et al., 2011).

(e) A super database needs to be established to collect data from multiple centers. This could fall under the auspices of CHARGE (Witsell et al., 2011) or built on the larger studies already designed and analyzed (Rauch et al., 2011). Online entering of data from participating clinics without patient identifiers could easily be done with a small investment, possibly funded by the National Institute on Deafness and Other Communication Disorders.

Hearing Loss that is Steroid-Responsive Proves it was Immune-Mediated

The main therapeutic application of glucocorticoids is for their immune suppressive and anti-inflammatory effects, and was first given in 1948 for rheumatoid arthritis (Flammer and Rogatsky, 2011). Their potential role in reversing autoimmune hearing loss was first tried in 1950 on a patient with colitis, although it was not clear if the steroid was responsible for the patient’s hearing recovery (Hilger and Goltz, 1951). Glucocorticoids were given routinely for autoimmune related ear disorders in the 1950s with some success (Smith, 1970). Thus, from the beginning, glucocorticoids have been assumed to restore hearing because of their immune suppressive and anti-inflammatory functions. Because of our inability to determine the actual inner ear pathology prior to treatment, or how it is reversed following treatment, there has been little evidence to argue against this. Thus, it is widely held today that autoimmune ear disease and other immune-mediated hearing disorders are caused by inner ear inflammation, the proof of which is demonstrated by response to steroid therapy. Thus the term “steroid-responsive hearing loss” is used virtually synonymously with immune-mediated hearing loss (Fig. 2). This rather circular logic is probably not always true, at several levels.

**Does autoimmune disease cause inner ear inflammation?**

The first arm of the steroid-responsive theory implies that if hearing loss occurs in autoimmune disease, it must be the result of inner ear inflammation (Fig. 2). Despite this common opinion, there is little evidence that autoimmune diseases cause inflammation of the inner ear. Temporal bones from autoimmune patients show little or no inflammation (Arnold, 1987; Nadol and McKenna, 1987; Keithley et al., 1998). However, they often show significant bone proliferation, usually a sign of vascular degeneration. Also, spontaneous autoimmune mice do not manifest inner ear inflammation, despite steroid-responsive hearing loss (Trune et al., 2000; Trune, 2001). What may be a more likely mechanism is that the systemic inflammatory factors disrupt vascular endothelial cell integrity and cause breakdown of the blood labyrinth barrier and endolymph ion homeostasis. A vascular etiology has been proposed for a number of steroid responsive disorders, including immune-mediated hearing loss (Dornhoffer et al., 1997; Amor Dorado et al., 2009; George and Pradhan, 2009; Kanzaki et al., 2009), Menière’s disease (Brookes, 1986; Derebery et al., 1991; Savastano et al., 2007; Kariya et al., 2009), and sudden hearing loss (Evans et al., 1988; Lazarini and Camargo, 2006; Psifidis et al., 2006; Merchant et al., 2008). Vascular disruption in the stria vascularis could explain a final common pathway and mechanism for a variety of steroid responsive hearing disorders.
Such a vascular theory fits with what we know about hearing and vestibular dysfunction in systemic autoimmune diseases. All known systemic autoimmune diseases have a very high incidence of inner ear disease, generally running 30–50%, and vascular etiology in the ear is often proposed since it is the common finding in such disease (Garcia-Berrocal and Ramirez-Camacho, 2002; Kastanioudakis et al., 2002; Mathews and Kumar, 2003; Roverano et al., 2006; Nacci et al., 2010). Many cases of autoimmune hearing loss occur as sudden hearing loss (Ottaviani et al., 1999; Cadoni et al., 2002; Garcia-Berrocal et al., 2003; Agrup, 2008; Amor Dorado et al., 2009; Deroee et al., 2009; Hervier et al., 2010). In fact, often the inner ear is the first organ affected in systemic autoimmune diseases, probably due to the fact that a mild vascular pathology is going to affect the ear faster than any other organ system. This is supported by inner ear studies of autoimmune disease mice where the primary defect in the inner ear is breakdown of the stria vascularis blood vessels (Trune et al., 2000), loss of blood labyrinth barrier integrity (Lin and Trune, 1997; Trune, 1997), loss of EP (Ruckenstein et al., 1999), and hearing loss (Trune and Kempton, 2001), all of which are restored by steroid treatments. This is demonstrated by the pathology stria vascularis capillaries in autoimmune mice and their recovery with both glucocorticoid (prednisolone) and mineralocorticoid (aldosterone) treatments (Fig. 4).

Thus, the vascular integrity of the cochlea is highly susceptible to circulating inflammatory factors. Any compromise of the endothelial cell blood labyrinth barrier would lead to hearing loss, but the barrier components are restored by glucocorticoids. Even cell mediated mechanisms proposed for the ear would involve disruption of the barrier to permit inflammatory cells access to cochlear tissues (Baek et al., 2006). This final common pathway is likely for a variety of hearing disorders that are steroid responsive, but does not have to cause inflammation within the cochlea itself in many cases.

**Do steroids only suppress inflammation in the ear?**

Another flawed arm of the steroid-responsive logic is that steroids have only anti-inflammatory functions in the ear (Fig. 2). There is no question that glucocorticoids have a significant impact on inflammatory factors and suppress the overall immune system (Flammer and Rogatsky, 2011). However, this steroid class also impacts multiple metabolic pathways, not just those related to immune suppression. So, what are steroids doing in the inner ear when they are given either systemically or transtympanically? Affymetrix gene array studies following systemic and intratympanic steroid treatments reveal ~17,500 genes in the mouse ear. A single therapeutic subcutaneous dose of dexamethasone will cause significant upregulation of 4,792 inner ear genes and downregulation of 4,632 genes at 6 hr (Trune et al., 2012). If the dexamethasone is given transtympanically, these numbers reach 9,118 and 5,781 respectively. Thus, 85% of inner ear genes are significantly affected by a single transtympanic dose of dexamethasone. Comparable numbers are seen with prednisolone given orally and
transtympanically. Thus, many of the inner ear’s ion homeostasis genes are impacted by steroid treatments and their restoration (Trune et al., 2011a) would have a major impact on hearing and vestibular recovery. Presumably much of this impact is due to the glucocorticoids binding to the mineralocorticoid receptor to regulate steroid responsive hearing loss (Trune et al., 2006). Thus, the immune suppressive role of glucocorticoids is probably overshadowed by their significant regulation of thousands of other inner ear genes that are responsible for maintenance of the endolymph and blood labyrinth barrier. The mineralocorticoid fludrocortisone, the synthetic aldosterone, also has been shown to be effective in Menière’s disease (Pappas and Banyas, 1991) and mice (Trune and Kempton, 2010). The recovery of stria vascularis following treatments with the mineralocorticoid aldosterone, which has no glucocorticoid receptor binding affinity, emphasizes the significance of these nonglucocorticoid driven molecular processes in the cochlea (Fig. 4).

**Does autoimmune hearing loss always respond to steroids?**

A third flaw in the steroid-responsive theory is that the hearing loss must have been autoimmune or immune-mediated if it responds to steroids (Fig. 2). Although autoimmune hearing loss is described as the prototypical steroid-responsive hearing loss, it is now apparent that the presence of serum autoimmune factors is not always predictive of a positive response to steroid therapy (Ottaviani et al., 1999; Cadoni et al., 2002; Garcia-Berrocal et al., 2003; Loveman et al., 2004; Hervier et al., 2010). Steroid responsiveness presumably relates to the damage in the inner ear, not the presence of circulating immune factors. Glucocorticoid responsiveness can also be influenced by genetic variations in interleukins and their receptors (Vambutas et al., 2009; Pathak et al., 2011). Thus, several autoimmune patients may have the circulating cytokine typical of this disease, but their steroid responsiveness depends on personal genetic factors.

Thus, despite the current dogma surrounding the principles of steroid-responsive hearing loss (Fig. 2), it appears that multiple arms of the theory are not always true. This emphasizes the need to revise certain clinical thinking about immune mediated hearing loss, how other “types” of hearing loss (Meniére’s disease, sudden hearing loss) may share more in common mechanistically with immune-mediated disorders of the ear, and try to determine the underlying pathology of the ear to better target therapeutic interventions. While the current classification scheme for hearing disorders may be convenient, focusing diagnoses on pathology may eventually prove to be more suitable for therapeutic interventions, whether by steroids or some other key factor critical for ear recovery.

**Studies needed.**

(a) To begin understanding the actual impact of steroids on the inner ear, combined Affymetrix-Proteomics assessments need to be conducted following treatments with the common therapeutic glucocorticoids. This will begin to elucidate the impact of current therapies on inner ear mechanisms. Recent studies of whole ear (above), cochlear explants (Maeda et al., 2010), or endolymphatic sac (Friis et al., 2011)
demonstrate this is now feasible and suitable for identification of steroid specific (or other hormone) processes.

(b) Vascular beds in the inner ear, particularly the lateral wall, need to be assessed for pathology, ability to withstand inflammatory insults, and how their critical functions are altered when the glycocalyx is compromised. Of particular importance will be their ability to maintain the blood labyrinth barrier during various disease processes known to cause reversible hearing loss.

(c) Comprehensive temporal bone studies of archival collections need to assess whether inflammatory cells actually enter the ear with these various forms of hearing loss (Merchant et al., 2005a,b). If not, then alternative theories need to be established to explain the mechanisms of vascular mediated hearing loss and then alter therapeutic approaches to better match the actual disease mechanisms present.

(d) Serum markers have been employed in some studies, but these parameters need to become a part of patient workup to differentiate potential subgroups that may be steroid resistant. A more comprehensive serum assessment needs to be made of patients before and after treatments to identify those markers that may be elevated during disease and/or suppressed by steroids. The recently revised Clinical Practice Guidelines for sudden hearing loss recommends against such additional laboratory testing because it is not cost effective, does not improve the management of patients, and has a high incidence of false positive results (Stachler et al., 2012). We respectfully disagree. First, there is no such thing as a false positive, it is simply a matter of identifying which serum factors are relevant and which are not. This insight will only come about by comprehensive serum analyses of patients before and after treatment. Second, given the inability to “biopsy” the ear, serum analysis is the next best approach and may actually be more relevant and informative. Lastly, our capabilities now of cost effective genetic testing (Shearer et al., 2010) and multiplex ELISA (Trune et al., 2011b) make such laboratory assessments of genes and serum factors practical, informative, and rapid. While it can be argued that these tests are not available for most physicians treating such patients, it does demonstrate the feasibility and timeliness of a comprehensive clinical study to screen such factors in a multi-institutional study. The field of otology cannot advance in the diagnosis and treatment of the many causes of hearing loss until such studies are done and become routine in patient workups.

(e) The high incidence of allergy with Ménière’s disease (Keles et al., 2004; Derebery and Berliner, 2010) needs to be further explored to differentiate circulating inflammatory markers as potential causes of inner ear dysfunction.

Glucocorticoid Therapy has no Inner Ear Tissue-Specific and Challenge-Specific Transcriptional Effects

Looking back on the history of glucocorticoid therapy, it is intriguing that it proceeded without (a) knowing if the target receptors are present in the inner ear, or (b) an understanding of the molecular mechanisms underlying its effects. For example, the use of glucocorticoids to treat hearing disorders began decades before it was known that the target receptors (glucocorticoid and mineralocorticoid) were present in the inner ear. Since then there have been numerous clinical and experimental reports that have assessed the efficiency of this treatment not only for immune-mediated auditory disorders but also against sudden deafness (Spear and Schwartz, 2011; Stachler et al., 2012), noise trauma (Tabera et al., 2006a; Tahera et al., 2007; van de Water et al., 2011), Menière’s disease (Phillips and Westerberg, 2011), tinnitus (Topak et al., 2009), ototoxicity (Murphy and Daniel, 2011), as well as trauma induced by insertion of cochlear implants (Chang et al., 2009). However, it is nearly impossible to make any conclusions about cellular targets from the different clinical studies because of the heterogeneous nature of the data (Topak et al., 2009). The various treatment protocols including doses and duration, means of defining the disease, and history of previous hearing and other health problems are some causes for inconsistencies between the studies. Knowing the location of these receptors in the inner ear will help understand which cell types that will directly benefit from glucocorticoid therapy. Moreover, knowing the cell types that express the receptors is important for understanding cell-specific signaling mechanisms and the target genes that are activated or inhibited by the treatment.

Further complicating the issue is that the mechanisms underlying glucocorticoid activation involve both the classical genomic pathways (i.e., DNA binding) and nongenomic mechanisms, which are more rapid (Lee and Marcus, 2002; Yukawa et al., 2005; Datson et al., 2008; Kim et al., 2009). Such nongenomic actions can regulate immune responses by interacting with T cells (Lowenberg et al., 2008). We are just beginning to understand how the more rapidly acting nongenomic mechanism is operating on the auditory organ (Lee and Marcus, 2002; Yukawa et al., 2005; Datson et al., 2008; Kim et al., 2009). Thus, the anti-inflammatory actions of glucocorticoids may involve nongenomic mechanisms, which may have important roles in the discovery of new drugs to treat these immune disorders. Recent findings have demonstrated that the rapid nongenomic mechanisms have effects on glutamate-mediated neurotransmission (Chauoloff and Groc, 2011).

The expression of glucocorticoid receptors is limited to the inner and outer hair cells, the spiral ganglion neurons and the spiral ligament (Rarey et al., 1993; ten Cate et al., 1993; Shimazaki et al., 2002; Shimazaki et al., 2002; Tahera et al., 2006a; Meltser et al., 2009). Furthermore, expression differs among these cell types: the spiral ganglion neurons have the highest expression, followed by the inner hair cells and the fibrocytes in the spiral ligament (Fig. 5). The outer hair cells are clearly positive, but have the least amount of expression. As a consequence, the effect of glucocorticoid therapy on the inner ear will have cell-type specific effects. Depending on the characteristics and pathology of the inner ear, glucocorticoid therapy may have vastly different outcomes. With regards to inflammation and inflammatory cells, it is known that monocytes have a high expression of the glucocorticoid receptor, while granulocytes have low
expression. It is known that the immunosuppressive action of glucocorticoids act also on primary and secondary immune cells through different mechanisms. Glucocorticoid therapy could result in either activating inflammation or by suppressing transcription factors involved in these signaling pathways due to the different receptor expression in these cell types.

Another aspect that is of particular interest for the auditory system concerns the central nervous system and the effects of glucocorticoid therapy. In the central nervous system, glucocorticoid receptors are abundantly and ubiquitously expressed in relatively high concentration (Reul and de Kloet, 1985). The mineralocorticoid receptors are more limited in the central nervous system and are localized primarily in the forebrain (Reul and de Kloet, 1985). It is therefore apparent that in the central nervous system the effects of glucocorticoid therapy will result in functional differences due to the location specificity of the two receptors. To date, there have not been any studies that have mapped out the expression of these receptors throughout the central auditory nervous system.

To optimize glucocorticoid therapy, a detailed account of the glucocorticoid action on different cell types in the inner ear is needed. Once this information is available we will then have the knowledge to develop cell-specific glucocorticoid agonists and antagonists. This development will not only help improve the efficiency of the therapy but should also be able to reduce unwanted side effects that are often found with prolonged treatment. It may also result in new therapeutic protocols that would lower the concentration of exogenous glucocorticoids and more specifically target the receptors and their downstream pathways. Finally, a detailed understanding of the genomic and nongenomic effects that occur in the different cell types in the inner ear would be very clinically beneficial.

Studies needed.

(a) To determine if the different glucocorticoid receptor-positive cell types in the inner ear have similar sensitivities and signaling pathways in response to glucocorticoid therapy. For example, if the spiral ganglion neurons have a higher expression of glucocorticoid receptors than the outer hair cells, would there be mechanistic differences in response to the application of exogenous ligand?

(b) A better understanding of what genes are altered by glucocorticoid therapy in different cell types in the cochlea. More cell-specific knowledge is needed for determining what protein–protein interaction occur with other transcription factors or if some of the activation is the result of direct gene transcription.

(c) To determine how specific glucocorticoid agonists and antagonists affect the different cell types in the inner ear. Since the expression of glucocorticoids varies among the different cells types could different pharmacological drugs have different actions on the different cells?

(d) There is no information regarding the effects of glucocorticoid therapy for different types of hearing loss. Experiments should be designed to determine if there are differential effects of glucocorticoid therapy depending on loss of inner versus outer hair cells, or if there is spiral ganglion damage? Animal models would be important to characterize these different situations.

(e) To determine how the activity of the enzyme, 11β-hydroxysteroid dehydrogenase, which is involved in the conversion of 11-deoxycortisol to cortisol, is regulated in the inner ear and if its activity is altered in inner ear disease.

(f) The circulating levels of cortisol in the blood is bound to a corticosteroid binding globulin which then controls the diffusion of corticosterone through the cell membrane. It would be important to understand the role of the binding globulin in different inner ear disorders and its interaction with drugs used for glucocorticoid therapy.

(g) To gain a better understanding of the molecular mechanisms underlying glucocorticoid receptor signaling in both normal and pathological inner ear tissues. At present, little is known about the glucocorticoid responsive element, chaperon complexes, and how they are changed in pathological situations.

(h) To determine if the membrane bound receptors, that govern the nongenomic actions of glucocorticoids, exist in the inner ear tissues. These receptors will need to be localized, physiologically characterized and pharmacologically assayed. Once this information is available ligand specific agonists and antagonists could then be developed for therapeutic purposes.

(i) To identify the location of glucocorticoid receptors throughout the central auditory pathway and
determine the responsiveness to glucocorticoid therapy. At present there is little known about the location of these receptors in the central auditory pathway and if they are modified in pathophysiological conditions.

A Fixed Regimen for Glucocorticoid Therapy is Effective for all Patients

There is relatively little variation in the dose used for glucocorticoid therapy despite the well-known fact that the endogenous secretion of glucocorticoids vary with the age, sex, physical and psychological stress levels of the individual, as well as time of day. While the synthesis and secretion of glucocorticoids is tightly controlled, it can also vary greatly among individuals partly because of the above mentioned reasons and these factors could be one underlying reason for why there is such a large individual response to glucocorticoid therapy. The cellular sensitivity to glucocorticoid therapy will be dependent on the availability of the endogenous hormone, the affinity and number of glucocorticoids in specific tissues, mineralocorticoid receptor availability and responsiveness of downstream target transcription factors. All of these factors are known to vary with age, sex, season, time of day and lifestyle (including diet, smoking, alcohol consumption, sleep patterns and physical activity). It is therefore difficult to understand how a fixed regimen for glucocorticoid therapy would be effective for all patients. The effects of age are apparent when studying the effects of stress responses. During aging obvious changes occur to the HPA axis where the levels of cortisol and glucocorticoid receptors decrease in the CNS (Sapolsky et al., 1984; de Kloet et al., 1991). As a consequence the overall effectiveness of glucocorticoid therapy will be different for young and old subjects, a factor that is presently not taken into account.

The most dramatic changes in cortisol occur throughout the day (Fig. 6). It is well known that endogenous glucocorticoids have a diurnal pattern with a peak occurring prior to awakening and a gradual fall to low levels in the evening. A practical consequence of this is that glucocorticoid therapy will have variable effects when delivered either in the morning (i.e., high cortisol levels), afternoon (i.e., moderate levels) or evening (low levels). During these different times of the day the ligand binding to the glucocorticoid receptors and subsequent activation of related enzymes and transcription factors will be widely different.

It is also known that there are clear sex differences in susceptibility to disease (Fig. 6). Research has indicated that this difference could be related to stress tolerance and stress responsiveness and suggests that stress is a risk factor for certain disorders. Men are more prone to arteriosclerosis (Kalin and Zumoff, 1990) and infectious disease (Klein, 2000), while women often suffer from autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis (Beeson, 1994). As a result of these stress-related diseases, glucocorticoid therapy will have different effects depending on the health of the individual and sex. As such, stress-related disorders and sex should be taken into consideration before glucocorticoid therapy is initiated.

With increasing age, the negative feedback mechanism of the HPA axis declines, resulting in prolonged elevations of cortisol. Prolonged elevation of cortisol leads to neurodegenerative and affective disorders affecting most prominently the hippocampus and the paraventricular nucleus due to the high concentration of the glucocorticoid receptor in these regions. It has even been shown that stress responses are prolonged in aged subjects, also causing prolonged elevations of cortisol (McEwen, 2000). The mechanisms responsible for the prolonged elevation after stress or the reduced negative feedback during aging is not known, but has been suggested to be due to vascular deficiencies, changes in turnover of the glucocorticoid receptor or by a reduction in transcription activity (Bamberger et al., 1996). The changes in biochemical activity of cortisol and the HPA axis with increasing age is complex and will indirectly influence the interventions by glucocorticoid therapy. Because of the prolonged elevation of glucocorticoids, it is feasible that the treatment could have detrimental effects on the auditory system combined with cognitive function.

Studies needed.

(a) To develop a simple test to identify the cortisol profile of candidates for glucocorticoid therapy. Knowing if an individual has a high or low cortisol profile would give the possibility to adjust the dose and duration of therapy to the individuals specific needs.

(b) Experimentally demonstrate how the effect of (i) sex, (ii) age, and (iii) stress levels influence glucocorticoid receptor expression and signaling mechanisms in the inner ear and in the central auditory nervous system.
system. This basic information will lay the foundation for improved glucocorticoid therapy.

(c) To determine how lifestyle (diet, smoking, alcohol consumption, sleep patterns, and physical activity) interferes with the effectiveness of glucocorticoid therapy. To date, there is no record of such information from clinical studies. Those individuals who are chronically stressed have altered sleep patterns that will be evident in their 24-hr cortisol profile. These individuals tend not to reduce their cortisol levels in the evening and can maintain higher levels throughout the day.

CONCLUSION

The therapeutic application of glucocorticoids for inner ear disorders is a complex and poorly understood field. We have little understanding of the role of steroids in the normal ear, and even less regarding the impact of steroids given clinically. While it remains the main treatment for a variety of hearing and vestibular disorders, we have little predictive insight as to whether it will be effective, and why it did or did not work. Trans-tympanic delivery of steroids has been a significant, though controversial, addition to the clinician’s armamentarium, but it has brought us no closer to an understanding of steroid-responsive mechanisms in the ear. Recent research shows glucocorticoids have a wide-spread impact on normal inner ear cellular and molecular processes, affecting many thousands of genes. Thus, therapeutic glucocorticoids appear to have a much broader impact on ear than once thought, not only mediated through the glucocorticoid receptor, but the mineralocorticoid receptor as well. Further complicating our efforts is the fact various other natural steroid hormones have specific roles in the ear. Thus, a glucocorticoid driven process may not even be the underlying cause of a patient’s inner ear dysfunction. It is our intention in this review to make the reader aware of what we know, what we do not know, and what can we do to fill gaps in our understanding. Development of better therapeutic approaches to ear disorders will happen, but it depends on significantly expanding our knowledge of these inner ear processes.

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