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How Useful Is Corticosteroid Treatment in Cochlear Disorders?

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Key Words

Cochlea · Sudden deafness · Sensorineural hearing loss · Noise-induced hearing loss · Ménière's disease · Tinnitus · Corticosteroids · Glucocorticoids · Mineralocorticoids · Auditory-evoked potentials · Cochlear blood flow · Perilymph pO_2 · Cochlear hypoxia

Abstract

The scientific basis for the administration of corticosteroids classified as glucocorticoids in certain cochlear disorders, such as immune-mediated progressive and idiopathic acute sensorineural hearing loss (SNHL), Ménière's disease and noise-induced hearing loss (NIHL), was discussed. The current knowledge on the physiological functions of endogenous glucocorticoids and the pharmacological effects of their synthetic analogs was summarized. Emphasis was placed on experimental studies on corticosteroids in the cochleovestibular system and on the therapeutic effects of glucocorticoids on SNHL, Ménière's disease, NIHL and chronic tinnitus obtained from clinical trials. Glucocorticoids exert numerous profound effects on almost every organ system, including mechanisms involved in anti-inflammatory action and immunosuppression. However, inflammatory tissue alterations are not only elicited by bacterial, viral or other immunopathological processes but also by physically and chemically induced cellular damage, tissue ischemia and hypoxia. Regardless of whether one or more of these insults underlie SNHL, Ménière's disease and NIHL, glucocorticoids effectively counteract subsequent inflammatory tissue damage in the auditory and vestibular system. This was confirmed in experimental studies on immune-mediated progressive SNHL, and thrombosis-induced and noise-induced cochlear ischemia, hypoxia and hearing loss. Glucocorticoid treatment results of immune-mediated progressive and acute idiopathic SNHL are promising, although placebo-controlled trials on the effect in acute idiopathic SNHL have revealed conflicting data (probably due to the small number of patients). Clinical studies on the effect of systemic glucocorticoid monotherapy on Ménière's disease and NIHL have not yet been performed. After intratympanic application, relief of vertigo, tinnitus and preservation of hearing in Ménière's disease was observed in previous studies; however, recently none of these effects have been confirmed in a placebo-controlled trial. Similarly, in contrast to previous reports, chronic tinnitus of various origins did not improve after repetitive glucocorticoid application onto the round window membrane using a micropump connected to an implanted microcatheter.

Wie nützlich ist eine Therapie mit Kortikosteroiden bei Innenohrerkrankungen?

Das Ziel dieser Arbeit bestand darin, die wissenschaftlichen Grundlagen für eine Therapie mit Glukokortikoiden bei unterschiedlichen Innenohrerkrankungen (progrediente immunassoziierte; akute idiopathische; Morbus Ménière; knall- und lärmbedingte) zu erläutern. Hierfür wurde eine zusammenfassende Übersicht über den aktuellen Kenntnisstand über die Wirkung endogener Glukokortikoide und ihrer synthetischen Derivate erstellt. Zudem wurden die vorliegenden experimentellen Studien über die Wirkung von Glukokortikoiden im kochleovestibulären System aufgeführt. Zum Schluss wurden klinische Studienergebnisse über die therapeutischen Wirkungen bei progredienten und akuten idiopathischen Innenohrerkrankungen, beim Morbus Ménière, bei knall- und lärmtraumatisch bedingten Innenohrschwerhörigkeiten und beim Tinnitus kritisch diskutiert. Glukokortikoide haben zahlreiche und vielfältige Wirkungen in nahezu allen Organsystemen. Am besten sind ihre antiphlogistischen und immunsuppressiven Effekte erforscht. Entzündliche Gewebeveränderungen sind jedoch nicht nur durch bakterielle oder virale Infektionen oder durch andere immunpathologische Mechanismen bedingt, sondern finden sich auch in mechanisch oder chemisch geschädigten sowie in ischämischen und hypoxischen Geweben. Insofern sollten Glukokortikoide unabhängig von den Pathomechanismen oben genannter kochleovestibulärer Erkrankungen ef-

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fektiv therapeutisch wirksam sein. Dies wurde in experimentellen Studien anhand von Tiermodellen für eine immunassoziierte progrediente Innenohrerkrankung und für ischämisch-hypoxische Innenohrerkrankungen nach photochemisch induzierten kochleären Thrombosen und nach Lärmeinwirkungen bewiesen. Die klinischen Ergebnisse einer Glukokortikoidtherapie bei progredienten immunassoziierten Innenohrerkrankungen und bei akuten idiopathischen Innenohrerkrankungen (sogenannter Hörsturz) sind erfolgversprechend. Allerdings haben sich in den vier bisher vorliegenden plazebokontrollierten Studien mit Hörsturzpatienten widersprüchliche Ergebnisse ergeben, u.a. auch durch die geringen Fallzahlen. Klinische Studien mit einer Monotherapie mit Glukokortikoiden bei Ménière-Patienten oder bei akuten Knall- und Lärmtraumata wurden bisher nicht durchgeführt. Nach intratympanaler Glukokortikoidapplikation bei Ménière-Patienten konnten frühere Erfolgsberichte hinsichtlich der vestibulären Beschwerden, des Hörvermögens und des Tinnitus in aktuellen plazebokontrollierten Studien nicht bestätigt werden. Ähnlich verhält es sich mit dem chronischen Tinnitus aufgrund unterschiedlichster Innenohrerkrankungen, der sich nach repetitiven Glukokortikoidapplikationen direkt auf die Rundfenstermembran mit Hilfe einer implantierten Mikropumpe nicht veränderte.

Quelle est l'utilité du traitement par corticostéroïdes dans les affections cochléaires?

Les bases scientifiques justifiant l'administration de corticostéroïdes, de la classe des glucocorticoïdes, dans diverses affections cochléaires, telles que les surdités progressives auto-immunes, les surdités brusques idiopathiques, la maladie de Ménière et les traumatismes acoustiques, sont discutées. Les connaissances actuelles des fonctions physiologiques des glucocorticoïdes endogènes et les effets pharmacologiques de leurs analogues synthétiques sont résumés sur la base d'études expérimentales et d'essais cliniques. Les glucocorticoïdes exercent de nombreux effets sur quasi tous les systèmes d'organes, incluant les mécanismes impliqués dans les processus anti-inflammatoires et l'immunosuppression. Cependant, l'inflammation tissulaire ne résulte pas seulement d'atteintes bactériennes, virales ou d'autres processus immunopathologiques, mais aussi de dommages cellulaires d'origine physique ou chimique, d'ischémie et d'hypoxie. Indépendamment du savoir si l'un ou l'autre de ces mécanismes est à l'origine des surdités brusques, de la maladie de Ménière ou des traumatismes acoustiques, il apparaît que les glucocorticoïdes empêchent les dommages tissulaires d'ordre inflammatoire qui en résultent, tant dans le système auditif que vestibulaire. Ceci a été démontré sur la base d'expériences sur les surdités résultant d'affections auto-immunes ou d'ischémie cochléaire par thrombose ou traumatisme acoustique. Les résultats du traitement par glucocorticoïdes des surdités progressives auto-immunes et des surdités brusques idiopathiques sont encourageants, bien que les études avec un groupe témoin traité par placébo donnent des résultats contradictoires, ceci probablement en raison du petit nombre de patients inclus. Les études évaluant l'efficacité des glucocorticoïdes en monothérapie dans la maladie de Ménière et les traumatismes acoustiques manquent. Quelques études ont rapporté que l'injection intratympanique permettait une cessation des vertiges et des acouphènes, tout en préservant l'audition. Toutefois, ces résultats n'ont pas été confirmés par une récente étude avec groupe témoin. Les acouphènes chroniques de diverses origines ne semblent pas diminuer par l'application répétée de glucocorticoïdes sur la fenêtre ronde.

Introduction

Synthetic analogs of corticosteroids classified as glucocorticoids (e.g. prednisolone) exert numerous profound effects on almost every organ system, including mechanisms involved against inflammation and in immunosuppression. However, inflammatory tissue alterations are not only elicited by bacterial, viral or other immunopathological processes but also by physically and chemically induced cellular damage, tissue ischemia and hypoxia [for reviews, see 1–4]. Therefore, glucocorticoids are among the most used pharmacological agents, regardless of whether the inciting agent is mechanical, radiant, chemical, ischemic, hypoxic, infectious or immunological.

Gucocorticoids have successfully been used for the treatment of immune-mediated progressive sensorineural hearing loss, idiopathic acute sensorineural hearing loss (SNHL), Ménière's disease and noise-induced hearing loss (NIHL), although neither the precise pathomechanisms underlying these cochlear disorders nor the mechanisms of drug action in the auditory system have been clarified. In this article, the authors attempt to provide a scientific basis for the administration of glucocorticoids in certain cochlear disorders. The physiological functions of endogenous glucocorticoids and the pharmacological effects of their synthetic analogs are reviewed. Emphasis will be placed on experimental studies on corticosteroids in the cochleo-vestibular system and on the therapeutic effects of glucocorticoids on immune-mediated progressive and idiopathic acute SNHL, Ménière's disease, NIHL and chronic tinnitus obtained from clinical trials.

Physiological Functions of Corticosteroids and Pharmacological Effects of Synthetic Analogs

Corticosteroids have multiple effects in a multitude of tissues. Therefore, we have summarized the current knowlege from the abundant literature in the following sections and refer to recent reviews [1–68].

Principal Pharmacokinetics and Pharmacodynamics

Endogenous Corticosteroids

The adrenocorticotropic hormone (corticotropin) released from the adenohypophysis stimulates the synthesis and release of two classes of steroids in the adrenal cortex: (1) the corticosteroids, classified as glucocorticoids and mineralocorticoids, and (2) the androgens.

The major glucocorticoids – the biologically active cortisol (hydrocortisone), the inactive metabolite cortisone and corticosterone, which has modest but significant glu-

cocorticoid and mineralocorticoid effects – alter the carbohydrate, protein and lipid metabolism, and have an inhibitory influence on inflammatory processes.

The major mineralocorticoid aldosterone primarily regulates electrolyte and water homeostasis.

The normal daily rates of production and secretion of the physiologically most significant corticosteroids cortisol and aldosterone are 8–25 and 0.15 mg/day, respectively. The circulating cortisol plasma levels are 16 μg/100 ml at 8 a.m. and 4 μg/100 ml at 4 p.m.; the aldosterone plasma level is 0.01 μg/100 ml. Circumstances of stress, such as injury, major surgery, hemorrhage, hypoglycemia, severe infection, cold, pain and fear lead to a marked increase (at least 10-fold) of the daily production rate of cortisol.

Synthetic Analogs of Glucocorticoids

Synthetic glucocorticoids are grouped according to their relative anti-inflammatory and sodium-retaining potencies related to the major endogenous cortisol and the synthetic cortisol analogs, respectively. Compared to cortisol, prednisone and prednisolone exert a 4-fold, methylprednisolone and triamcinolone a 5-fold, and betamethasone and dexamethasone a 25-fold anti-inflammatory effect. Compared to the value 1 for cortisol, the Na^+-retaining potency of prednisone and prednisolone is 0.8, and 0.5 for methylprednisolone, while triamcinolone, betamethasone, and dexamethasone do not have Na^+-retaining effects. Fludrocortisone exerts a 10-fold anti-inflammatory and a 125-fold sodium-retaining potency.

The biological half-life of cortisol and fludrocortisone is 8–12 h, while it lasts 12–36 h after administration of prednisone, prednisolone, methylprednisolone and triamcinolone, and 36–72 h after betamethasone and dexamethasone application.

Synthetic glucocorticoids with an 11-keto substituent, such as cortisone and prednisone, require enzymatic activation in the liver before they are biologically active. This does not account for 11β-hydroxysteroids, such as cortisol and prednisolone.

95% of cortisol and 40–60% of prednisolone are reversibly bound in the plasma to corticosteroid-binding globulin (transcortin) and albumin; however, at supraphysiological concentrations, a greater fraction is unbound. Only unbound glucocorticoids may enter the cells. It is known that after systemic administration of 300 mg prednisolone, glucocorticoid receptors are fully saturated in humans [34].

Long-term use of synthetic glucocorticoids may be associated with more or less pronounced undesirable side effects, such as fluid and electrolyte abnormalities, hypertension, increased risk of infections, hyperglycemia, osteoporosis, myopathia, cataract, gastric ulcers, growth arrest in children, fat redistribution, striae, ecchymoses, acne, hirsutism and disturbances in mood and behavior. In addition, systemic allergic reactions to corticosteroids may occur [69, see further literature in 69].

Cellular Genome-Mediated Effects (within 1–2 h)

Binding by Intracellular Corticosteroid Receptors

Endogenous glucocorticoids bind with equal affinity to both, glucocorticoid and mineralocorticoid receptor proteins, the first of which present in the cytoplasm of virtually all mammalian cells, the latter of which expressed in the kidney, colon, salivary glands, sweat glands, CNS and in the cochleovestibular system (see the sections on their expression below).

Synthetic glucocorticoids, such as synthetic cortisol, prednisone, prednisolone, methylprednisolone and fludrocortisone, also bind to both receptor types (with various affinity, see section on synthetic analogs of glucocorticoids), while triamcinolone, betamethasone and dexamethasone exclusively bind to glucocorticoid receptors.

The inactive glucocorticoid receptor is a complex of several proteins in the cytoplasm, including the heat shock proteins HSP 90 and HSP 70, and a 56-kD immunophillin. The basic structure and principles of action of the mineralocorticoid receptor appear to be similar, although it has been studied in less detail. Upon corticosteroid binding the receptor complex undergoes a series of structural modifications and translocation to the nucleus, where it binds to specific DNA sequences to change transcription factors and the levels of synthesized proteins.

The Enzyme 11β-Hydroxysteroid Dehydrogenase

In order to protect the mineralocorticoid receptor from the much higher circulating concentrations of glucocorticoids, cortisol and corticosterone are metabolized in certain tissues (particularly in the kidney and in the brain) by the enzyme 11β-hydroxysteroid dehydrogenase to receptor-inactive 11-keto derivatives, such as cortisone and 11-dehydrocorticosterone. Recent studies have demonstrated tissue-specific isoforms of the enzyme, some of which catalyse the reverse conversion of cortisone to cortisol. So far, the isozymes modulate ligand binding to glucocorticoid and mineralocorticoid receptors, thereby amplifying and attenuating the tissue-specific response. Furthermore, recent findings indicate that both receptors interact by forming heterodimers, thereby increasing the functional diversity of corticosteroid action, including responsiveness to neurotransmitters, neurosteroids and neuroendocrine control.

Effects after Binding to Corticosteroid Receptors

Binding by glucocorticoid receptor proteins, expressed in virtually all mammalian cells, results in:

– inhibition of the formation and liberation of proinflammatory mediators, such as eicosanoids (prostaglandins, prostacyclin, thromboxanes, leukotrienes and platelet-activating factor), and cytokines (interleukins 1 to 12, interferon α and γ, tumor necrosis factor α, growth factor GM-CSF);
– furthermore, adhesion and transendothelial migration of inflammatory cells from the circulation into affected areas are inhibited as a consequence of glucocorticoid-induced inhibition of the elaboration and/or action of lymphokines and specific receptor molecules on endothelial cells, leukocytes and monocytes;
– in addition, glucocorticoids inhibit the activity of proteolytic enzymes, such as collagenase and stromelysin;
– recently it has been shown that glucocorticoids at high doses protect against free-oxygen-radical-mediated cellular damage by their antilipid peroxidative effects;
– glucocorticoids are also thought to down-regulate the transcription and activity of inducible nitric oxide synthase, thereby inhibiting the production of nitric oxide, a gaseous neurotransmitter, neuromodulator, immune mediator and vasodilator;
– the mechanisms by which glucocorticoids stimulate gluconeogenesis from amino acids and glycerol, promote deposition of glucose as liver glycogen, inhibit glucose utilization, increase protein breakdown and activate lipolysis resulting in an alteration of fat distribution in peripheral tissues are not fully defined yet;
– furthermore, total body calcium stores are depleted by interfering with Ca^{2+} uptake in the gut and Ca^{2+} excretion in the kidney by unknown mechanisms;
– glucocorticoids also increase the expression of adrenergic receptors in vascular smooth muscle cells, which may contribute to arterial hypertension, such as the mineralocorticoid-receptor-mediated Na^+ and fluid retention (see below); however, the precise underlying mechanisms remain to be elucidated;
– this also accounts for muscle weakness, which may either be induced by mineralocorticoid-receptor-mediated K^+ excretion (see below) or by glucocorticoid-receptor-mediated protein breakdown with consequent skeletal muscle wasting;
– and finally, elevated levels of glucocorticoids (whether induced by systemic administration, sustained physical or social stress, or accompanied by psychiatric, neurological and other disorders) are associated with structural changes in specific brain areas enriched with glucocorticoid and mineralocorticoid receptors, and with dysregulation and dysfunction of these receptors, thereby affecting neurochemical transmission, neuroendocrine control and mood and behavior. After systemic administration, some patients exhibit euphoria, insomnia, restlessness and increased motor activity, others become anxious, depressed or even psychotic.

Binding by mineralocorticoid receptor proteins, expressed in multiple central and peripheral tissues, including the vestibulocochlear system, results in:

– enhanced synthesis and activation of the enzyme Na,K-ATPase, thereby influencing intra- and extracellular osmolarity, electrochemical gradients across the cell membrane and neuronal conduction;
– in addition, the number of open Na^+ and K^+ channels is increased by an unknown mechanism;
– renal reabsorption of Na^+ from the tubular fluid is enhanced with consequent expansion of the extracellular fluid volume contributing to arterial hypertension, while the urinary excretion of K^+ and H^+ is increased.

Cellular Nongenomic Effects (within Minutes)

In contrast to the classical delayed genomic effects, recent studies have documented that corticosteroids may also interact with specific membrane-bound proteins, such as ligand-gated ion channels (specifically, the $GABA_A$ receptor) and G-protein coupled receptors. Evidence for these nonclassic rapid actions is available for all steroids and for a multitude of tissues, including central and peripheral neurons. Binding to membrane-associated steroid receptors results in activation of the sodium/proton exchanger and second-messenger systems, such as phospholipase C, phosphoinositide turnover, intracellular pH and Ca^{2+} as well as protein kinase C. This, in turn, alters the permeability for certain cations (e.g. Ca^{2+} ions), changes site-specific neurotransmitter concentrations and neuronal activity, attenuates lipid peroxidation by free oxygen radicals, and activates ATP-mediated biochemical processes. The precise mechanisms involved have not been clarified yet.

Experimental Studies on Corticosteroids in the Cochleovestibular System

Expression of Glucocorticoid Receptors

Rarey and Luttge [70] first identified glucocorticoid receptor proteins in rat cochlear and vestibular tissue samples in 1989. In human cochlear and vestibular tissue specimens, glucocorticoid receptors were first detected by Rarey and Curtis in 1996 [71].

In rats, the highest glucocorticoid receptor levels were observed in type I and III fibrocytes in the spiral ligament, in spiral limbus cells, in the organ of Corti region, and in spiral ganglion cells, while the receptor levels in the stria

vascularis and in the endolymphatic sac region were intermediate, and the lowest levels were measured in vestibular dark cells, the cristae ampullares and maculae utriculi [72–74]. Similarly, in guinea pigs the glucocorticoid receptor concentration in the lateral cochlear wall exceeded that in the ampulla of the semicircular canal [75]. The receptor expression during development in the rat [76] and in CBA mice [77] indicates a tissue- and age-specific nonlinear curve up to postnatal days 14–21, when an adult pattern was observed.

After immobilization stress, glucocorticoid receptor levels of rats increased in spiral ligament tissues and decreased in the organ of Corti, while the levels in stria vascularis tissues remained unchanged [78].

After noise stress (white noise, 85 dB SPL, 4 h on 3 consecutive days), glucocorticoid receptor levels of rats remained unchanged in spiral ligament tissues and decreased in the organ of Corti [79].

In cultured cochlear and vestibular tissues, glucocorticoid conditioned media induced changes in protein synthesis [80].

Expression of Mineralocorticoid Receptors

Rarey and Luttge [70] first identified mineralocorticoid receptor proteins in rat cochlear and vestibular tissue samples in 1989. The receptor was localized within the rat marginal cells, spiral ligament, spiral limbus, outer and inner hair cells, spiral ganglion cells and cochlear nerve [81, 82]. In the guinea pig, receptor proteins were evident in the vascular stria, spiral prominence and spiral ligament [83, 84] and in the ampullae of the semicircular canals [85].

Expression of HSPs

The inactive glucocorticoid and mineralocorticoid receptor is a complex of several proteins, including HSP 90 and HSP 70, and a 56-kD immunophillin (see above).

HSP 90 is constitutive in inner and outer hair cells of rats, and the levels are initially decreased and then increased after exposure to broad-band noise (110 dB SPL, 90 min) in both cell types [86].

The HSP 70 family (constitutive HSP 70, present in cells under normal conditions; inducible HSP 72) was detected in many cochlear cell types of unstressed and heat-stressed guinea pigs [87–91]. Furthermore, hyperthermia-induced nuclear transition of HSP 70 was demonstrated [90].

However, the HSP 70 family was not detectable in unstressed rats [89, 92], but HSP 72 synthesis was induced by heat stress in strial vessels, the spiral ligament, the spiral limbus and in spiral ganglion neurons [89]. Similarly, following varying periods of unilateral cochlear ischemia and reperfusion, HSP 72 could be detected in rat cochlear homogenates [92]. And finally, HSP-72-immunoreactive staining was also observed in rats, exposed to 110 dB SPL broad-band noise for 90 min, in the cytoplasm of outer hair cells and few inner hair cells, and stria vascularis, but not in supportive cells and spiral ganglion cells [86, 93]. However, Western blot results showed HSP 72 also in spiral ganglion cells and cochlear nerve [86].

Expression of the Enzyme 11β-Hydroxysteroid Dehydrogenase

Various tissue-specific isoforms of the enzyme 11β-hydroxysteroid dehydrogenase metabolize cortisol and corticosterone to inactive derivatives (e.g. cortisone) and vice versa. Thereby the mineralocorticoid receptor is protected from the much higher circulating concentrations of glucocorticoids, and ligand binding to glucocorticoid and mineralocorticoid receptors is modulated (see above).

11β-hydroxysteroid dehydrogenase is colocalized with glucocorticoid and mineralocorticoid receptors in the spiral ligament of rats, while other cochlear regions and the vestibular membranous labyrinth were devoid of the enzyme [94]. The expression appeared on the 12th postnatal day with strong expression on day 15 [95] and was therefore preceded by the expression of glucocorticoid receptors [76]. In guinea pigs, the enzyme has been localized in the ampullae of the semicircular canal [96].

Expression of the Enzyme Na,K-ATPase

Corticosteroids regulate sodium and potassium ion transport through regulation of Na,K-ATPase, a process mediated by mineralocorticoid receptors, which bind endogenous and certain synthetic glucocorticoids and mineralocorticoids (see section on binding by intracellular corticosteroid receptors).

The expression of Na,K-ATPase was early suggested in the mammalian cochleovestibular system, and recently heterogeneous expression of the subunit isoforms has been detected in several mammalian species in the stria vascularis (marginal cells, intermediate cells), spiral ligament fibrocytes, spiral limbus fibrocytes, interdental cells, outer sulcus epithelial cells, pillar cells, base of inner and outer hair cells (probably rather the neurilemma of afferent but not that of efferent nerve processes beneath hair cells), cochlear nerve fibers, type I spiral ganglion neurons and their central and peripheral processes, endolymphatic sac, crista ampullaris and macula of the saccule, dark cells of the ampullae and utricle, and in the sensory regions of

the vestibular end organs [85, 97–130; for a review, see 131]. The presence of Na,K-ATPase was also (indirectly) established in isolated outer hair cells by measurements of membrane potentials [132] and in distinct fibrocytes of the spiral ligament, and in the stria vascularis by measuring the intracellular Na^+ concentration [133]. Normal immunoreactivity for Na,K-ATPase was also observed in cultured marginal cells [134] and in mice with a null mutation of the glucocorticoid receptor [128].

It is interesting to note that an age-dependent degeneration and loss of immunoreactivity and specific activity of Na,K-ATPase was observed in gerbil and rat strial marginal cells and spiral ligament fibrocytes [111, 120, 126, 127]. Furthermore, immunoreactivity of certain isoforms of Na,K-ATPase in the stria vascularis, spiral limbus, spiral ganglion cells and cochlear nerve is increased in hyperthyroid states and decreased under hypothyroid conditions and is responsive to triiodothyronine treatment [125]. And finally, catecholamines and serotonin may also control Na,K-ATPase activity in strial marginal cells [135–140].

Changes due to Altered Levels of Endogenous Corticosteroids

The morphological integrity of the cellular architecture of the stria vascularis [141–143] and the ampullar dark cells [141, 144, 145] is dependent on an adequate plasma corticosteroid level in rats. When diet-induced mineralocorticoid deficiency is substituted with aldosterone, the number of Na^+,$K(^+)$-ATPase sites in the lateral cochlear wall and in the ampullae of the semicircular canal is increased in guinea pigs [85].

In adrenalectomized rats, glucocorticoid substitution increased Na,K-ATPase levels in the stria vascularis and spiral ligament, while mineralocorticoid substitution increased only strial enzyme levels [112].

Potassium concentration in the perilymph, endolymph, marginal cells and spiral ligament, and endolymphatic potentials remained unchanged in adrenalectomized rats, although potassium levels in the plasma of adrenalectomized rats were higher compared to normal rats [146, 147].

Similarly, endolymphatic and perilymphatic sodium and potassium concentrations, and endolymphatic potential, were not changed in adrenalectomized rats whether supplementation with dexamethasone was performed or not [148].

Free calcium concentration was reduced in the plasma of adrenalectomized rats but increased in the perilymph and spiral ligament, while no change was observed in strial marginal cells and in the endolymph [149].

Adenosine triphosphatase activity was decreased in the stria vascularis, spiral ligament and ampullar dark cells, but not in utricular dark-cell tissues in adrenalectomized rats [141].

Noise-induced (100 dB SPL, 30 min) elevation of auditory nerve compound action potential (CAP) thresholds was similar in adrenalectomized and normal rats, and endolymphatic potassium concentration and endolymphatic potential were not affected by noise in both groups [146].

Effects of Synthetic Glucocorticoids in Normal Animals

Glucocorticoids Applied Locally onto the Round Window Membrane

After repetitive (once a day for 5 consecutive days) transtympanic injection of cortisol into the round window niche of rats, auditory brainstem response (ABR) thresholds were impaired in the frequency range of 12–31.5 kHz but not in the range of 2–8 kHz. ABRs did not recover until 8 weeks after application. Morphological intracochlear damage as assessed by light and transmission electron microscopy was not observed [150].

However, after single transtympanic injection of dexamethasone into the round window niche of guinea pigs, cochlear blood flow increased until the end of the recording period after 60 min, without any significant change of ABRs and intracochlear morphology until 4 weeks after application [151].

Systemically Applied Glucocorticoids

The effect of prednisolone, either at low (2.5 mg) or high doses (25 mg) on cochlear blood flow, the partial pressure of oxygen (pO_2) in the perilymph, cochlear microphonics (CMs), CAPs of the auditory nerve and ABRs was examined in guinea pigs [152]. After 10 min intravenous infusion time, recordings were continued for further 110 min. Peripheral cardiovascular parameters, cochlear blood flow, CMs, CAPs and ABRs did not change significantly, but perilymph pO_2 showed a significant decrease after infusion of both prednisolone doses. In contrast, controls monitored for 210 min and isotonic-saline-infused animals did not show any significant change of the measuring parameters [152–156]. It remains to be seen whether oxygen-consuming mechanisms, by which glucocorticoids act to mobilize amino acids for gluconeogenesis and alter glucose utilization, or nongenomic effects that are supposed to activate ATP-mediated biochemical processes can explain the poor effect on perilymph pO_2.

Effects of Synthetic Glucocorticoids in Experimental Cochlear Damages

Salicylate Ototoxicity

After pretreatment with dexamethasone, salicylate-induced hearing loss as assessed by ABRs was partially prevented in chinchillas [157]. The authors assumed that the dexamethasone-induced increased levels of prostaglandins and decreased levels of leukotrienes observed in the perilymph contributed to the effect.

Photochemically Induced Focal Cochlear Microcirculation Lesions

After pretreatment with a synthetic cortisol analog, the photochemically induced decrease in blood flow in the lateral cochlear wall and the area of stria vascularis degeneration was significantly attenuated [158]. The authors suggested that cortisol may have prevented the production of free oxygen radicals, which are generated when intravenously infused rose bengal is photoactivated using a xenon lamp. This is known to damage the vascular endothelium with subsequent thrombosis.

Immune-Mediated Progressive SNHL

Deterioration of ABR thresholds of 20-week-old MRL/MP-lpr/lpr mice, bred for the study of autoimmune disease [159], was prevented by daily prednisolone treatment for 10 weeks [160].

Noise-Induced Hearing Loss

After exposure to broad-band noise (6–30 kHz) of 120 dB SPL for 5 min, and methylprednisolone treatment 15 min prior to the noise exposure, with 4 additional doses being given at 8-hour intervals, the ABR threshold shift of F_1 hybrid offspring of inbred mice strains was significantly smaller in the high frequencies compared to untreated controls [161].

After exposure to broad-band noise of 100 dB SPL twice over 24 h, pretreatment with prednisolone before the second exposure brought about a significantly more pronounced recovery of CAP thresholds of the auditory nerve in guinea pigs [162].

After exposure to 2-kHz pure tones of 110 dB SPL for 10 min and daily postexposure treatment with methylprednisolone for 7 days, the CAP threshold shift of guinea pigs was significantly smaller compared to saline-treated controls at all frequencies tested (2–16 kHz). However, after exposure to 115 and 120 dB SPL, treatment with methylprednisolone was ineffective [163].

After exposure to 1/3 octave band noise centered at 8 kHz of 129 dB SPL for 20 min, recovery of CAP threshold shifts (2–32 kHz) was significantly improved, and cochlear damage as assessed by cochleograms was much smaller in methylprednisolone-treated (daily for 5 days) guinea pigs as compared to untreated controls up to 14 days after exposure [164].

After exposure to broad-band noise (1–12 kHz) of 106 dB SPL for 30 min, single treatment with a low prednisolone dose (2.5 mg) resulted in recovery of CAPs, but CMs, ABRs and cochlear blood flow did not differ significantly from untreated and isotonic-saline-treated guinea pigs up until the end of the recording period at 180 min after exposure. Similarly to the unexposed prednisolone-treated animals, perilymphatic pO_2 showed a significantly greater decrease compared to the values in the noise-exposed, untreated animals [152, 155].

In contrast, after single treatment with a high prednisolone dose (25 mg), perilymphatic pO_2 values did not significantly differ from the noise-exposed untreated group. This also applied to the cochlear blood flow values; however, the therapeutic effect on the auditory function was significant. Amplitudes significantly increased with partial recovery of CMs and full recovery of CAPs and ABRs already 50 min after termination of infusion and remained stable for further 60 min until the end of the recording period at 180 min after exposure [152, 155].

It is interesting to note that glucocorticoid treatment using a high prednisolone dose did not relieve progressive noise-induced cochlear hypoxia and posttraumatic ischemia but resulted in partial recovery of CMs and full recovery of CAPs and ABRs [152, 155]. These findings indicate direct cellular effects of prednisolone in the noise-damaged cochlea taking into account no blood flow and oxygenation. The possible mechanisms involved are discussed elsewhere [152]. Experimental studies have further shown that NIHL is also effectively treated after noise exposure with another anti-inflammatory agent, diclofenac sodium, although impaired cochlear blood flow and perilymphatic pO_2 did not improve, as with prednisolone [152, 155]. Furthermore, a combination therapy of prednisolone together with hyperbaric oxygen (inhalation of 100% oxygen at an elevated ambient pressure of 2.6 atmosphere absolute in a hyperbaric chamber) achieved even better results [154, 155, 164]. Isobaric oxygen therapy (inhalation of 100% oxygen at normal ambient pressure) was less effective [154, 155] or not effective at all [164], such as carbogen gas (95% O_2 + 5% CO_2) [164].

Drill-Induced Ossicular Chain Injury

Pretreatment with methylprednisolone did not prevent a permanent CAP threshold shift due to standardized drill-induced injury to the guinea pig incus until a 5-week observation period [165].

Clinical Results of the Therapeutic Effect of Glucocorticoids in Cochlear Disorders

Immune-Mediated Progressive SNHL

Progressive SNHL is supposed to be immune mediated and can be successfully treated with long-term administration of glucocorticoids [166–172; for recent reviews, see 173–177].

Idiopathic Acute SNHL

Clinical studies on the effect of glucocorticoids on idiopathic acute SNHL have revealed somewhat conflicting results. In the literature many reports are available about positive experiences with glucocorticoid treatment. However, patients received simultaneously additional agents, such as blood-flow-promoting drugs, lidocaine, vitamins and others. Therefore, it is difficult to estimate whether glucocorticoids have contributed to recovery of hearing or not. Furthermore, according to the results of placebo-controlled clinical trials and those in which the outcome of no treatment was compared with the effect of various drugs (including glucocorticoids, see below), the rate of spontaneous partial recovery lies between 32 and 89%, with spontaneous full recovery of 25–68% [for recent reviews and literature, see 178–180].

Concerning the effect of glucocorticoids in comparison to placebo or no treatment, only four clinical trials have been performed [172, 181–183]. Mattox and Simmons [181] came to the conclusion that 20 of 28 nontreated patients (71%) recovered their hearing 'completely or a good percentage', and 63 of 88 patients (72%) showed similar results after glucocorticoid therapy. Wilson et al. [182] reported that of 52 nontreated patients, 29 cases regained normal hearing ability (i.e. 56%). Excluding those patients with a middle-frequency hearing loss, since a spontaneous recovery was always demonstrated [182], 17 of 35 nontreated patients with a low- or high-frequency hearing loss were found to have regained their hearing ability 3 months at the latest following onset of affliction (i.e. 49%). In contrast, 11 of 34 placebo-treated patients recovered their hearing (i.e. 32%), while 20 of 33 glucocorticoid-treated patients (i.e. 61%), particularly those with moderate hearing loss, showed similar results. Moskowitz et al. [183] deduced that 24 of 27 glucocorticoid-treated patients (i.e. 89%) 'recovered at least 50% of their hearing', whereas 4 of 9 patients (i.e. 44%) recovered their hearing without any treatment. Veldman et al. [172] have found an effective response to glucocorticoid treatment in 6 of 12 patients (i.e. 50%), while only 6 of 19 nontreated patients (i.e. 32%) showed similar results. In order to statistically compare the results with no treatment or placebo therapy with those obtained with glucocorticoids, the numbers of patients in both groups need to be equal. Furthermore, the number of patients in each group is too low in order to express recovery rates in percent. Therefore, it is still to be seen whether glucocorticoids are more effective than no treatment or placebo therapy in SNHL.

Ménière's Disease

Experimental and clinical studies indicate that immune-mediated mechanisms may be involved in Ménière's disease [for recent reviews, see 176, 177, 184–187]. Positive experiences with systemic glucocorticoid treatment of Ménière's disease have been reported; however, patients received additional agents, and placebo-controlled clinical trials have not been performed. However, the effectiveness of intratympanically applied glucocorticoids without supplements has been evaluated [188–193]. Previous results have indicated effectiveness for vertigo in almost all treated ears and amelioration of tinnitus in most ears but no improvement of hearing [188, 189]. Preliminary results from recent studies indicate good relief of dizzy spells and preservation of hearing in many patients [190, 191]. In another study, hearing improved in 5, did not change in 7 and deteriorated in 3 of 15 ears [192]. In contrast, no significant changes were observed in any measured parameter (hearing loss, tinnitus, aural fulness and caloric vestibular response) in 20 patients who had either received placebo or dexamethasone on 3 consecutive days [193].

Noise-Induced Hearing Loss

Clinical results on the effect of glucocorticoids in noise-induced hearing loss have not yet been published.

Tinnitus

Placebo-controlled clinical results on the effect of systemically applied glucocorticoids on tinnitus have not yet been published.

In early reports, amelioration of tinnitus was observed after intratympanic glucocorticoid injection in most ears of patients suffering from Ménière's disease [188, 189]. In contrast, no effect on tinnitus has recently been established in 20 patients suffering from Ménière's disease who had either received intratympanic application of placebo or dexamethasone on 3 consecutive days [193].

Tinnitus associated with various cochlear disorders was abolished in 87, considerably ameliorated in 39 and not changed in 14 of 140 ears of 109 patients who had received a single intratympanic glucocorticoid injection

[194]. In contrast, benefit was not confirmed in a small-scale trial with 6 patients [195]. In a recent report [196], tinnitus was completely eliminated in 3, reduced in 5, unchanged in 5 and worse in 1 of 14 patients suffering from various inner ear diseases after repetitive intratympanic glucocorticoid administration. In contrast, Lenarz et al. [197] have not observed any improvement of tinnitus in 20 patients suffering from various cochlear disorders after repetitive glucocorticoid application onto the round window membrane using a micropump connected to an implanted microcatheter. The other drugs tested in this study (lidocaine, gentamycin, glutamate, glutamate receptor antagonists) were also ineffective. In summary, the use of intratympanic glucocorticoids should remain investigational until more experimental and clinical data about the long-term effects after repetitive application are available [198].

Conclusions

The rationale for administration of anti-inflammatory agents, such as glucocorticoids in immune-mediated progressive and idiopathic acute SNHL, Ménière's disease and NIHL is based on the following considerations.

Inflammatory tissue alterations are not only elicited by bacterial, viral or other immunopathological processes but also by physically and chemically induced cellular damage, tissue ischemia and hypoxia [1–4]. Therefore, regardless of whether one or more of these pathomechanisms underlie SNHL, Ménière's disease and NIHL, glucocorticoids effectively counteract the subsequent inflammatory tissue damage in the auditory and vestibular system. Bioelectrical changes in the cochlea and retrocochlear auditory system evolving during immunological and/or physical and/or ischemic-hypoxic cellular pathomechanisms become apparent as hyperpolarization, failure of synaptic transmission, neuronal K^+ loss and uptake of large amounts of Na^+, Cl^- and Ca^{2+}, accompanied by H_2O, causing cellular swelling and biochemical and bioelectrical dysfunction [for a review, see 131]. These and more pathological changes on the cellular level are targets for the glucocorticoid and mineralocorticoid receptor-mediated delayed genomic actions, and the membranous receptor-mediated rapid nongenomic actions of glucocorticoids. The receptors are evident in all physiologically most significant cochlear and vestibular cells. The enzyme 11β-hydroxysteroid dehydrogenase, involved in the modulation of glucocorticoid binding to glucocorticoid and mineralocorticoid receptors, was detected. And, finally, activation of the enzyme Na,K-ATPase distributed widely in the cochlea and peripheral vestibular system subsequent to binding of endogenous and certain synthetic glucocorticoids to mineralocorticoid receptors has been proved. These findings are the essential basis for therapeutic effects of glucocorticoids in the cochleovestibular system, such as activation of carbohydrate and protein metabolism involved in cellular recovery processes and protection from further cellular damage. In addition, synthetic glucocorticoids which also bind to mineralocorticoid receptors will contribute to the restoration of disturbed cellular osmolarity, electrochemical gradients and neuronal conduction. Evidence for these effects comes from experimental studies, which have demonstrated that salicylate ototoxicity, damage and thrombosis of strial vessels due to free oxygen radicals and immune-mediated progressive SNHL are prevented by pretreatment with glucocorticoids. Furthermore, it has been shown that NIHL recovers after postexposure treatment with prednisolone (a synthetic glucocorticoid which binds to both glucocorticoid and mineralocorticoid receptors), although progressive noise-induced cochlear hypoxia and posttraumatic ischemia were not relieved. Clinical studies on the effect of glucocorticoid monotherapy on NIHL have not yet been performed. Treatment results of immune-mediated progressive and acute idiopathic SNHL with glucocorticoids are promising, although placebo-controlled trials on the effect in acute idiopathic SNHL have revealed conflicting data so far. A greater number of patients is needed in order to obtain valid statistical results. Systemic glucocorticoid treatment of Ménière's disease is recommended and is being widely used; however, it is difficult to estimate how much glucocorticoids have contributed to the therapeutic effects, since patients have received other drugs simultaneously. Monotherapy with intratympanically applied glucocorticoids have indicated relief of dizzy spells, amelioration of tinnitus and preservation but no improvement of hearing in earlier reports, but none of these effects have recently been observed in a placebo-controlled study. Similarly, in contrast to previous studies, chronic tinnitus associated with various cochlear disorders did not improve after repetitive glucocorticoid application onto the round window membrane using a micropump connected to an implanted microcatheter. The other drugs tested in this recent study [197], such as lidocaine, gentamycin, glutamate and glutamate receptor antagonists, were also ineffective.

In summary, experimental and clinical results on the therapeutic effect of glucocorticoids in immune-mediated progressive and idiopathic acute SNHL, Ménière's disease and NIHL are promising; however, this should be confirmed in further controlled clinical trials.

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Comments

E. Hultcrantz (Sweden): This is a very valuable report on the pharmacological effects of glucocorticosteroids on the audiovestibular system. I will greatly benefit from this paper. I especially noticed that glucocorticosteroids could protect against free radicals and inhibit the production of nitric oxide. The first is probably a good thing for a patient with sudden deafness and the second could be a disadvantage. The experiments on normal animals do not show clear-cut results, and much more needs to be done to explain the presence of steroid receptors everywhere in the cochlea. The experiments with steroids in damaged ears seem very interesting and demonstrate a direct cellular effect without influencing blood flow or oxygenation.

However, hyperbaric oxygen could improve the results further. After these exciting results from animal experiments, one might expect that the treatment of patients with sudden deafness would be at least possible to evaluate! But that is not easy, because of the high spontaneous recovery rate, the small number of patients in each study and the study designs. The conclusion of this paper is that we need more controlled clinical studies to prove the maybe nonspecific effect of steroids on sudden deafness. I can only agree. Perhaps we should start an EU project?

J. Kanzaki (Japan): Several sources suggest that glucocorticoids have some beneficial effects on inner ear disorders, such as idiopathic sudden sensorineural hearing loss (ISSNHL) and Ménière's disease. These positive reports have been supported by numerous research studies. In regard to ISSNHL, however, we so far have only sporadic studies on the efficacy of glucocorticoids using double-blinded control trials. Unfortunately so far only a limited number of subjects have been registered in each trial. It is therefore necessary to conduct a large-scale control trial in order to establish the efficacy of glucocorticoids on ISSNHL.

P. Tran Ba Huy (France): This paper presents a remarkable review of the present knowledge on corticosteroid treatment in various inner ear disorders. Of great interest are the studies on the expression of glucocorticoid receptors and of some enzymes in the cochleovestibular system. These data must be considered when proposing a therapy in SNHL as they represent a basis for administration of anti-inflammatory agents in idiopathic SNHL. Yet, I question the feasibility of controlled clinical trials.