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Electrocochleography in Guinea Pigs

Negin Salehi*[1] and Farzaneh Zamiri Abdollahi[2]

[1]*Phd student of audiology, Iran University of Medical Science, Iran*

[2]*Phd of audiology, Tehran University of Medical Sciences, Iran*

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***Corresponding author:** Negin Salehi, Phd student of audiology, Iran University of Medical Science, Iran Tel: 009822228051; Email: Salehi_au@yahoo.com

Abstract

Electrocochleography is the best electrophysiological measurement for cochlear condition investigation in guinea pig models. In this article, we will review new issues in recording electrocochleography in guinea pigs in two parts including measurement parameters and clinical applications.

Keywords: Electrocochleography; Guinea Pig; The cochlea

Abbreviations: EcohG: Electrocochleography; CAP: Compound Action Potential; CM: Cochlear Microphonics; SP: Summating Potential; AP: Action Potential; SGNs: Spiral Ganglion Neurons; FFT: Fast Fourier transformation; DC: Direct Current

Introduction

Due to tremendous difficulties associated with human experiments on auditory system, such as dissection hardness due to stiff temporal bone, animal models are the best choice for studies on the cochlear physiology. Researchers have shown that range of small mammals like cat, chinchilla, guinea pig, rat, and mouse, are appropriate options for providing insight into the human cochlear physiology. Guinea pigs are one of the classic models in auditory research due to extensive similarities in hearing range and the cochlea's structure with the humans. Many years ago, Georg von Bekesy described the mechanics of cochlea in guinea pigs. On the other hand in 2003, the successful efforts in regenerating the hair cells were done in guinea pigs [1].

One of the best ways of studying the auditory system and specially the cochlea in these animals is recording auditory evoked responses. They represent activity within the auditory system that is stimulated or evoked by sounds. These recordings play a vital role in the identification and diagnosis of auditory system pathologies. Electrocochleography (EcochG) is the earliest auditory evoked response and its components arise from the inner ear and auditory (8th cranial) nerve fibers near the inner ear (distal end of 8th nerve). It is considered as the most advantageous electrophysiological potentials in documentation of cochlear status [2].

Researchers all over the world have investigated the cochlear condition in multiple guinea pig's peripheral auditory system disorders models via EcochG. This article will review the most important measurement parameters as well as clinical applications of EcochG in guinea pigs.

The goals of recording EcochG in Guinea pigs

One of the main applications of recording EcochG in guinea pigs is better understanding physiology of the auditory system, specially the cochlea. EcochG has several beneficial applications in cochlear physiology studies including studying the role of different channels in mammalian cochlea [3-5], cochlear micromechanics such as nonlinearity [6], possible roles of nitric oxide [7] and effects of changing perilymphatic K+ in the cochlea [8].

Another goal of recording EcochG in guinea pigs is determining the underlying mechanism of cochlear diseases, such as endolymphatic hydrops [9-12], hyperbilirubinemia [13,14], noise-induced hearing loss [15,16], cochlear ischemia [17], perilymphatic fistula [18] and hidden hearing loss [19]. Studying effects of various drugs on cochlear function is the next goal for recording EcochG in guinea pigs. For instance, investigating influence of drug-induced ototoxicity on cochlear function such as cisplatin [20-24], Quinine [25] and ethyl benzene [26], the effect of blood flow promoting drugs [27], the effect of anesthetics such as isoflurane [28], histamine and its antagonists [29], and the effect of a dopaminergic agonist in cochlear physiology and physiopathology [30].

Stimulus type

Three different types of stimuli have been used in articles for recording the EcochG response. Two most dominant stimuli are Clicks and Tone burst. Clicks consisted of biphasic alternating acoustic pulses (100 μs/phase)[18,28] and 100ms electrical pulse [17]. Tone bursts included Trains of 8 [10,20,21,26,28] or 10 [9,13,14,29] ms probes, with frequencies of 2-32KHz. The probes had cosine-shaped rise and fall times of 4 ms at 0.5 kHz, 2ms at 1kHz, 1.5ms at 2kHz and 1ms at the higher frequencies [9,10,13,14,17, 18,20,21,26,28,29]. In one research with the aim of study of CM latency, audiometric tones of 250, 500, 1000, 2000 and 4000 Hz were used [31].

Electrode locations

Two main electrode arrays can be used in recording EcochG parameters in guinea pigs. One of them, which is called "round window approach", is the most widespread method for yielding optimal and high quality recordings of the CM, SP, and AP. Animals are anesthetized by an intraperitoneal injection of anesthetics and are placed in a head holder. Body temperature is maintained by a heating pad at 37 °C [16]. Cochlea is exposed through a dorsal approach [32]. Once the skin and muscles are incised behind the ear, bulla is opened and the round window of the cochlea is exposed [33]. An Ag-Cl-electrode is placed at the round window niche of the ear. Reference and ground electrodes are usually placed on the skull [34,35] or neck musculature [36]. In studies which recording the EcochG response is repeated in multiple time intervals, the electrode is chronically implanted at round window [37].

To measure cochlear responses from either the scala vestibuli or the scala tympani, after using appropriate anesthetic agent, the animal's head is guarded dorsally in stereotactic machinery. The bony frame of bulla is opened and a 0.2mm hole is made into the cochlea. The electrode is made of a Teflon coated Ag-Cl recording wire which is placed on scala vestibuli or the scala tympani [4,9,12,21,38].

It is possible also to record the EcochG components by placing the active electrode on posterior superior wall of the external ear canal near the tympanic membrane, and reference and ground electrodes on the vertex and the frontal region respectively [11].

Waveform Analysis

There are plenty of procedures for analyzing the latency, threshold and amplitude of EcochG components. CAP waveforms are analyzed by determining the amplitude, latency and threshold of the first and second negative peaks (N1 and N2). The CAPs threshold is usually defined as the lowest intensity stimulus which evokes a specific magnitude of CAP (0.5mV) [10,26]. There is also an alternative method which uses a software algorithm and is based on adjusting the level of stimulus until the response is just visually noticeable above the noise floor of the recording [9]. Most researchers use peak to peak amplitude method for analyzing CAP amplitude, as the voltage difference between the first negative peak after stimulus onset (N1) and the following positive peak [9,10,13]. While the others believe that as the CAP is principally superimposed on the SP, the amplitude of the CAP (N1) must be measured relative to the SP and not relative to the base line of the recording or the next positive peak [20,26,28].

Using the FFT in a window from stimulus onset to 2ms after offset [28], applying a first-order Boltzmann equation to the CM waveform in the second half of the CM waveform [9], or measuring peak-to-peak amplitude in the middle of the sinusoidal response [20] are various techniques of assessing CM amplitude. Measuring the response a few milliseconds after the onset of stimuli is to avoid contamination from CAP [13].

SP can be observed as the DC shift in round window potential occurring both at the onset and offset of the tone and there are arguments for and against using either as the SP measure [39,40]. The onset SP could be under-estimated because of the start of the negative-going N1 wave of the CAP, whereas the slower slope of the offset SP is probably the result of contamination by changes in asynchronous neural firing [41]. To overcome these issues, SP amplitude is measured as the difference between the pre-response baseline potential and the DC level from approximately 5.5-6.5ms following stimulus onset [20], to be concurrent with the relatively stable plateau after the CAP [10].

Clinical Applications

Endolymphatic Hydrops (EH): Injecting artificial endolymph into scala media in anaesthetized guinea pigs is as an acute model of endolymphatic hydrops [42]. With injecting volumes up to 1-2μl endolymph, results in fundamental changed in EcochG recording parameters. These changes includes an increase in CAP threshold specially at low frequencies [43], an increase in SP amplitude, and also a change in the asymmetric distortion of the CM, resulting from a shift in the nonlinear electro-mechanical transduction [44,45]. Researchers have suggested a mechanism underlying these changes. That is, Reissner's membrane is swelled into scala vestibuli and the organ of Corti is dislocated toward the scala tympani due to increase in hydrostatic pressure of the endolymph [46]. These cases modify cochlear sensitivity and nonlinear mechano-electrical transduction [47]. But when the injected volume increases to 3μl, a fast and sudden recovery of the changes is observed, which is highly similar to the clinical findings observed in Meniere's Disease [9]. Receiving dexamethasone can prevent the reported EcochG findings in experimentally-induced endolymphatic hydrops [11].

Hyperbilirubinemia

Guinea pigs are considered as worthy animals in modeling human cases with hyperbilirubinemia, as their auditory system is immature at birth, and this is a good characteristic in matching these models with preterm neonates with hyperbilirubinemia [13]. To establish the hyperbilirubinemia model, animals

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received an intraperitoneal injection of bilirubin at 100mg/kg [48].

The EcochG shows normal CM, elevated CAP threshold, and significantly prolonged peak latencies and duration. These results suggest that hyperbilirubinemia in neonatal guinea pigs impaired auditory peripheral neuromechanisms that targeted mainly the IHC synapses, the myelin sheath of SGNs and their fibers, and there is a potential relationship between hyperbilirubinemia and auditory neuropathy [13]. Receiving taurine, a 2-amino-ethanesulfonic acid, which is an abundant sulfur containing amino acid present in the inner ear in mammals [49], limits bilirubin-induced neural damage in the auditory system, which is revealed by significant attenuation of EcochG abnormalities [14].

Noise Induced Hearing Loss (NIHL)

Because of high similarities in hearing range between guinea pigs and humans, these small mammals have considered as NIHL model in several researches. The pathogenic mechanisms of noise-induced cochlear damage could be analyzed via EcochG response. The temporary threshold shift as well as permanent threshold shift is reflected in EcochG response as an increase in CAP Threshed and latency [15], and decrease in CM amplitude [16]. The protective effects of antioxidants such as N acetylcysteine on noise induced hearing impairment, is monitored effectively by investigating the changes in EcochG parameters [15].

Noise exposures that result in reversible changes in cochlear neural threshold can cause a reduced neural output at supra-threshold acoustic stimuli. This so-called "hidden hearing loss" [50], is associated with a selective loss of synapses between IHCs and the high threshold and low spontaneous rate population of primary afferent neurons [51]. EcochG is the best electrophysiological measure for either OHC or IHC and auditory nerve output. Persistent depression of the amplitudes of both CAP and SP in response to supra-threshold sounds is the prominent occurrence which happens in hidden hearing loss, which is representative of IHC-afferent synapse as well as hair cell malfunction [19].

Perilymphatic fistula (PLF)

Making a crossed incision on the round window membrane of guinea pig is a known way for modeling perilymphatic fistula. This procedure makes several changes in EcochG components, including SP and AP amplitude reduction and latency increase, and increases in the SP/AP ratios. The proposed mechanism for the changes which are observed by this intervention is related to attenuation in the afferent nerve fibers activity, as well as anatomic and functional chance in hair cells behavior, specially their active cochlear mechanism [18].

Cochlear Ischemia

An experimental local ischemia model of the guinea pig cochlea is reported frequently in literature. In this method, mechanically compressing anterior inferior cerebellar artery results in reduction of cochlear blood flow. The degree of induced cochlear ischemia is correlated with the alternations in N1 and N2 parameters of EcochG. As CAP of the cochlear nerve are sensitive to anoxia or ischemia, lower rate of cochlear blood flow is related to shorter survival time of N1 and N2 or prolongation of their latencies [17].

Conclusion

Guinea pigs are good animal models for human cochlea and they can help test different hypothesis, disease effects on cochlea, and treatments for diseases.

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