博士論文の要旨及び審査結果の要旨

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学位授与の日付　令和4年3月23日
学位授与の要件　学位規則第4条第1項該当
博士論文名　Electrochemical properties of the non-excitable tissue stria vascularis of the mammalian cochlea are sensitive to sounds.
（哺乳類の蝸牛の非興奮性組織である血管条の電気化学的特性の音に対する感受性）

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博士論文の要旨

Background and purpose

Endolymph, a unique extracellular solution in the cochlea of the mammalian inner ear, exhibits [K+] of ~150 mM and +80 mV. These unique electrochemical properties are maintained by a variety of K+ channels and transporters in non-excitable epithelial-like tissue, stria vascularis, which is functionally made up of double layers. Upon mechanical stimulation by sounds, K+ in the endolymph enters into sensory hair cells, exciting them. The highly positive endolymphatic potential accelerates for the K+ entry, sensitizing hearing. Subsequently, K+ exits the hair cells into the perilymph and recycles back to the endolymph via the stria vascularis. It is suggested that this unidirectional K+ transport constitutes a continuous current through the cochlea in the radial direction, which is referred to as 'cochlear circulating current'. This circulating current likely regulates the strial [K+] and potential dynamics, which determine the positive endolymphatic potential. Despite such conventional concept, it remains unclear whether and how acoustic stimulation affects the electrochemical properties of the stria vascularis. To address this longstanding enigma, the applicant focused a cochlear portion for the best frequency, 1 kHz and analyzed the strial electrochemical properties by in silico and in vivo approaches.

Methods

The theoretical analysis was carried out by the computational model, which has been previously developed by the applicant's group. This model integrates ion channels and transporters in the stria and hair cells into an electrical circuit and describes a circulation current composed of K+.

To physiologically examine the stria vascularis, the double-barreled needle-type K+-selective microelectrode was inserted into a fenestra made in the cochlear bony wall of anesthetized guinea pigs, and it was advanced across the stria vascularis towards the endolymph using a micromanipulator. This method simultaneously measured the potential and [K+] in vivo. While the electrode was held inside the stria vascularis , each animal was exposed to a series of acoustic stimuli composed of a sound of 1000 Hz for 10 s. The stimulation was repeated multiple time, and basically the average values were subjected to further analysis.

Results

In the computational model, mimicking of hair cells' K+ flow induced by a 1 kHz sound modulated the circulation current and affected the strial ion transport mechanisms. The latter effect resulted in monotonically decreasing potential and increasing [K+] in the extracellular strial compartment. This observation was never obtained when the stria vascularis and hair cells were electrically separated. The [K+] and potential alternations similar to the data simulated with the model were obtained when the stria in acoustically stimulated animals was examined by means of the double-barreled microelectrodes. In the stria, the measured potential dynamics was quantitively accounted for by the change of the [K+].

Consideration

This work for the first identified that the electrochemical properties of the stria vascularis can dynamically respond to acoustic stimulation. The result further indicates that the stria is electrically coupled to hair cells and this linkage underlies the cochlear circulation current.

(482 words)

審査結果の要旨

内耳の蝸牛に存在するユニークな細胞外溶液である内リンパは、高い[K+]と高い電位（+80 mV）というユニークな電気化学的性質を示す。内耳では音を感知する際に感覚有毛細胞が興奮するが、K+は、内リンパから有毛細胞へ入り、さらに、外リンパ、血管条を経由して内リンパへ戻る。この蝸牛循環電流は、血管条のK+チャネルとトランスポーターによって維持されていると考えられてきたが、音響刺激が血管条の電気化学的特性に影響を与えるかどうか、またどのように影響を与えるかは不明であった。そこで申請者は、in silico および in vivo のアプローチにより、血管条の電気化学的特性を解析した。理論的な解析は、以前に開発した fi-NHK 計算モデルを用いて行った。1000Hz の音による音響刺激を受けたモルモットの血管条を二重管式微小電極で調べたところ、計算モデルでシミュレーションしたデータと同様に音響刺激に応じた電位変動が得られた。血管条で測定された電位ダイナミクスは、[K+]の変化で定量的に説明された。

本論文は、血管条の電気化学的特性が音響刺激に動的に応答することを初めて確認し、実験結果のメカニズムを計算モデルによるシミュレーションで理論的に説明したことに学位論文としての価値を認める。