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Research paper

Evidence that the compound action potential (CAP) from the auditory nerve is a stationary potential generated across dura mater

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ABSTRACT

We have investigated the generation of the compound action potential (CAP) from the auditory nerve of guinea pigs. Responses to acoustic tone-bursts were recorded from the round window (RW), throughout the cochlear fluids, from the surface of the cochlear nucleus, from the central end of the auditory nerve after removal of the cochlear nucleus, from the scalp vertex, and from the contralateral ear. Responses were compared before, during and after experimental manipulations including pharmacological blockade of the auditory nerve, section of the auditory nerve, section of the efferent nerves, removal of the cochlear nucleus, and focal cooling of the cochlear nerve and/or cochlear nucleus. Regardless of the waveform changes occurring with these manipulations, the responses were similar in waveform but inverted polarity across the internal auditory meatus. The CAP waveforms were very similar before and after removal of the cochlear nucleus, apart from transient changes that could last many minutes. This suggests that the main CAP components are generated entirely by the eighth nerve. Based on previous studies and a clear understanding of the generation of extracellular potentials, we suggest that the early components in the responses recorded from the round window, from the cochlear fluids, from the surface of the cochlear nucleus, or from the scalp are a far-field or stationary potential, generated when the circulating action currents associated with each auditory neurone encounters a high extracellular resistance as it passes through the dura mater.

1. Introduction

The compound action potential (CAP) from the auditory nerve is measured clinically in humans, either trans-tympanically on the round window or boney prominence, or more recently from the surface of the tympanum (Ferraro and Durrant, 2002; Noguchi et al., 1999 ; Brown, 2007). In this study we have investigated the generation of this response in guinea pigs, monitoring the CAP at the round window, within the cochlea, within the braincase or at the surface of the scalp, while disrupting auditory nerve function with either direct mechanical pressure or chilling of the auditory nerve as it exits the internal auditory meatus and travels to the brainstem.

During the 1970s clinicians began to use changes in the CAP as a diagnostic measure of several cochlear nerve pathologies, such as vestibular schwannoma or Meniere's disease (Beagley and Gibson, 1976; Gibson and Beagley, 1976), but such electrocochleography (ECochG) became progressively less popular, partly due to improvements in MRI and OAE, partly due to the invasiveness and variability of the ECochG technique, and partly due to the lack of a clear understanding of the link between the changes in the CAP and the underlying pathologies. Currently ECochG is mainly used for detailed objective paediatric assessment, by some in the diagnosis of Ménière's disease (where the ratio of CAP to summating potential or SP amplitude is considered important), and in monitoring peripheral hearing function during cochlear nerve surgery.

Unfortunately there is still a poor understanding of how the CAP is generated, and what any changes in CAP waveshape might indicate about cochlear or auditory nerve function (Ferraro and Durrant, 2002), although in 1958 Goldstein and Kiang (1958) described the CAP waveform as the weighted, summated

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Abbreviations: RW, Round Window; CAP, Compound Action Potential; ECochG, Electrocochleography; SP, Summating Potential; UP, Unitary Potential; IAM, Internal Auditory Meatus; CN, Cochlear Nucleus; TTX, Tetrodotoxin; ABR, Auditory Brainstem Response; PSTH, Peri-Stimulus Time Histogram; LOCS, Lateral Olivocochlear System; MOCS, Medial Olivocochlear System.

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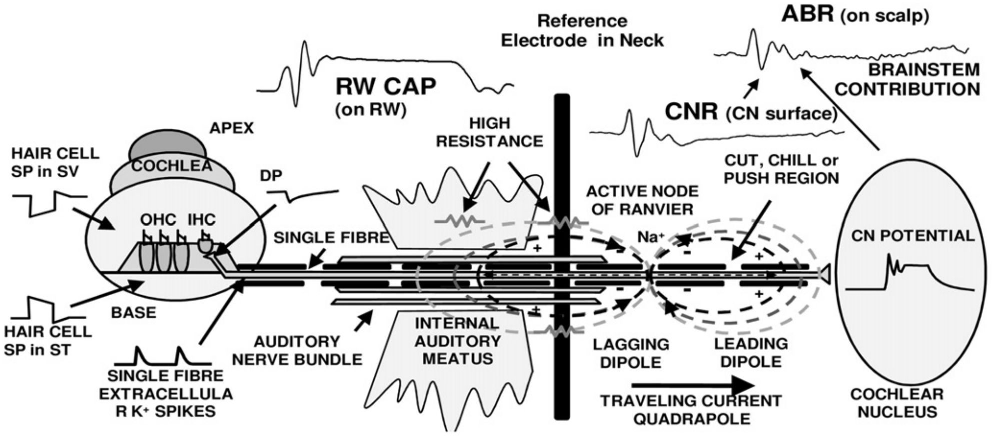

Fig. 1. An illustration of the generation of the cochlear and braincase neural potentials as the travelling quadrapole of nerve action currents encounter the high resistance of the IAM and dura mater. In the normal animal, when the leading dipole of the quadrapole encounters the distal opening of the IAM or the dura mater, it generates the first peak ($N1_{rw}$) of the round window CAP (RW CAP) and the first peak of the braincase response ($P1_{cn}$). Then, as the leading dipole encounters the proximal opening of the IAM, or as the lagging dipole encounters the dura mater, the action currents generate second inverted peaks at both locations ($P1_{rw}$ and $N1_{cn}$). At the cochlea these peaks add to the locally generated hair cell signals: the SP and the cochlear microphonic (not shown) which are antiphase in scala tympani and scala vestibule. The dendritic potential (DP) from the afferent neurones beneath the inner hair cells also adds to the composite signal within the cochlea. The neural signal in the braincase (the CNR) adds to smaller and later components from the brainstem to produce the much smaller ABR signal on the scalp. Experimental manipulations such as cutting, chilling and applying pressure to the VIIIth nerve have be performed on the proximal end of the nerve in the braincase in this study. The sample waveforms shown are actual responses from subsequent figures.

extracellular response generated by individual neurones firing synchronously at the onset of an acoustic stimulus. The single neurone contribution to the extracellular electrical population response (the compound action potential or CAP) as it fires once is referred to here as the *unitary potential* (UP; referred to earlier by Kiang et al. as the N_0 response), and has been estimated in a number of studies by either (a) back-averaging the extracellular electrical activity triggered by spikes from single VIIIth nerve neurones (Kiang et al., 1976; Wang, 1979; Versnel et al., 1992), (b) theoretically, using the frequency characteristics of the CAP and the ensemble neural noise (de Boer, 1975; McMahon and Patuzzi, 2002), or (c) by measuring the CAP with and without acoustic masking the CAP with filtered noise, and then estimating single fibre contributions with progressive subtraction (Elberling, 1976). Apart from their amplitude, the UP and CAP obtained in those experiments were similar in waveshape, with the CAP measured at the round window (RW) resembling a damped 1 kHz sinusoid (Fig. 1), consisting of a series of three to four interleaved negative and positive peaks, here termed $N1_{rw}$, $P1_{rw}$, $N2_{rw}$ and $P2_{rw}$, and so on. The analogous peaks in the response measured within the braincase (and near the CN when it is intact) are here termed $P1_{cn}$, $N1_{cn}$, $P2_{cn}$, $N2_{cn}$, and so on.

Even though the CAP waveform appears to be a weighted version of the UP waveform, there is still no clear understanding of how the UP is itself generated. It might be generated by ‘local’ near-field action currents (like the CAP recorded from the surface of a long nerve bundle), and/or a far-field potential (similar to the auditory brainstem response or ABR, recorded from the scalp). If the RW CAP consists of auditory nerve activity within the cochlea, then it could be used clinically to indicate abnormal peripheral generation of action potentials. On the other hand, if it contains components generated in the brainstem, it might provide a tool for diagnosing central pathologies or failed transmission between the cochlea and the brainstem.

To date, there have been three main views on the origins of the CAP. First, early studies suggested that the CAP recorded at the round window (RW) was generated at the internal auditory meatus (IAM), because the IAM is an electrical partition representing ‘a physiological electrode’ (Tasaki et al., 1954; Legouix and Pierson, 1974; Elberling, 1976; Teas et al., 1962). This early phrase ‘physiological electrode’ was used in the sense of a ‘sucrose gap electrode’ (Huxley and Stampfli, 1951; Stämpfli, 1954; Stys and Kocsis, 1995) commonly used to study neurones before the development of glass microelectrodes[1]. Both Tasaki et al. (1954) and Legouix and Pierson (1974) suggested that the CAP also included components generated near the recording electrode (near-field components), which were responsible for the differences in amplitude of the positive peaks in different cochlear turns.

Second, observations during surgery have suggested that the $P1_{rw}$ and $N2_{rw}$ peaks might be generated in the brainstem (Daigneault, 1974; Møller, 1983; Møller, 2000; Sellick et al., 2003). This view was primarily based on the observation that when the cochlear nucleus (CN) was removed, or the central end of the cochlear nerve was sectioned, the $P1_{rw}$ peak was abolished and the $N1_{rw}$ and $N2_{rw}$ peaks appeared to merge to produce one broad negative peak (Møller, 1983; McMahon and Patuzzi, 2002; Sellick et al., 2003). Furthermore, the response evoked by a high-frequency tone-burst measured at the surface of the CN also included a negative peak ($N1_{cn}$) and a positive peak ($P2_{cn}$) that followed the intial $P1_{cn}$ peak, and had absolute latencies similar to the positive $P1_{rw}$ and negative $N2_{rw}$ peaks in the CAP waveform.

Third, it has been suggested that the CAP contained some local components produced by action currents generated at the peripheral ends of the primary afferent neurones (McMahon et al., 2004; Brown et al., 2004). Specifically, it was suggested the $N1_{rw}$ peak was generated by Na^+ influx, and the $P1_{rw}$ peak might be generated by K^+ efflux from primary afferent cochlear nerves. This was supported by previous studies where the application of voltage-gated K^+ channel blockers to the cochlear nerve abolished the $P1_{rw}$ peak (van Emst et al., 1996), and by micropipette recordings from beneath the myelin sheath of VIIIth nerve neurones (Robertson, 1975) where the K^+ channels are localized (Chiu and Ritchie, 1981), which consisted of positive peaks similar to the $P1_{rw}$ peak in the CAP (Eng et al., 1988).

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[1] Certainly Tasaki worked with one of the pioneers of the sucrose gap technique (Stämpfli, 1954). Nevertheless, at the time the generation process of the auditory CAP was not clearly described, and is possibly less well understood today.