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Noradrenergic modulation of brainstem nuclei alters cochlear neural output

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Abstract

The peripheral auditory sense organ, the cochlea, receives innervation from lateral and medial olivocochlear neurons in the brainstem. These neurons are able to modulate cochlear neural output. Anatomical studies have shown that one of the neurotransmitters which is present in varicosities surrounding the olivocochlear neurons in the brainstem is noradrenaline and previous work on brainstem slices has demonstrated a generally excitatory effect of noradrenaline on medial olivocochlear neurons. In order to assess *in vivo* the function of the noradrenergic inputs to olivocochlear neurons, we injected noradrenaline in the brainstem of anaesthetised guinea pigs and recorded ipsilateral cochlear electrical activity. Injections of noradrenaline close to the lateral olivocochlear neurons evoked increases in the sound-driven neural activity from the cochlea, measured as compound action potential (CAP) amplitude, as well as in the spontaneous activity, measured as amplitude of the 900 Hz peak of the spectrum of the neural noise in the cochlear fluids. In contrast, noradrenaline in the vicinity of the medial olivocochlear neurons evoked inhibitory effects on both the CAP amplitude and 900 Hz peak. These results indicate most likely an excitatory action of noradrenaline on both the lateral and medial olivocochlear neurons in the brainstem, and show that such noradrenergic inputs can modulate cochlear function.

Keywords: Noradrenaline; Superior olivary complex; Hearing; Olivocochlear efferents; Guinea pig

1. Introduction

The mammalian cochlea receives innervation from the superior olivary complex within the brainstem. These olivocochlear neurons can be subdivided into a lateral and medial system. Lateral olivocochlear neurons originate in or around the lateral superior olive and project to the auditory afferent fibres contacting the inner hair cells of the organ of Corti. Medial olivocochlear neurons originate in the peri-olivary regions of the superior olivary complex and project to the outer hair cells in the organ of Corti (Warr and Guinan, 1979; White and Warr, 1983; Robertson, 1985; Robertson et al., 1987; Liberman and Brown, 1986; Vetter and Mugnaini, 1992).

Olivocochlear neurons can modulate cochlear neural output and could play an important role in key auditory processes such as optimising the detection of acoustic signals of interest in the presence of competing background noises.

The medial system has long been known to have an inhibitory effect on cochlear neural output, affecting the outer hair cells, which are responsible for the cochlear

Abbreviations: BDA, biotinylated dextran amine; CAP, compound action potential; LOC, lateral olivocochlear; LSO, lateral superior olive; MNTB, medial nucleus of the trapezoid body; MOC, medial olivocochlear; MSO, medial superior olive; NA, noradrenaline; PB, phosphate buffer; SNN, spectrum of the neural noise; SOC, superior olivary complex; SPN, superior paraolivary nucleus; VNTB, ventral nucleus of the trapezoid body

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gain (Desmedt, 1962; Wiederhold and Kiang, 1970; Brown and Nuttall, 1984; Kemp and Souter, 1988; Rajan, 1988a,b; Warren and Liberman, 1989a,b; Ruggero and Rich, 1991; Giraud et al., 1995).

The lateral system, because of its termination on primary afferent dendrites, is in a position to directly affect both spontaneous and sound-driven neural firing, independent of cochlear micro-mechanical gain. Indeed, a number of physiological studies have demonstrated both excitatory and inhibitory effects of the lateral system on cochlear neural output (Liberman, 1990; Walsh et al., 1998; Ruel et al., 2001; Groff and Liberman, 2003; Mulders and Robertson, 2005) but its biological function remains as yet unknown.

That the olivocochlear system is not just a simple isolated feedback system is suggested by both anatomical and physiological studies showing that higher brain centres, such as the inferior colliculus and auditory cortex provide input to the olivocochlear neurons (Thompson and Thompson, 1993; Vetter et al., 1993; Feliciano et al., 1995; Mulders and Robertson, 2000a,b). Previously, we have demonstrated in rats that the locus coeruleus provides noradrenergic input to both the lateral and medial olivocochlear neurons (Mulders and Robertson, 2001) and similar observations were made in guinea pig (unpublished results). Moreover, *in vitro* experiments in our laboratory on rat brainstem slices have demonstrated that noradrenaline exerts a direct, generally excitatory action on medial olivocochlear neurons (Wang and Robertson, 1997a,b).

In the present study, we set out to investigate *in vivo* the effects of noradrenaline application in the guinea pig superior olivary complex on cochlear neural output, in order to reveal whether the noradrenergic input to the olivocochlear system is capable of altering the auditory afferent information entering the brain. We measured two parameters of cochlear neural output; sound-driven response and spontaneous activity. The former was measured using the compound action potential of the auditory nerve (CAP) and the latter using the spectrum of the neural noise (SNN) (Dolan et al., 1990; Cazals and Huang, 1996; McMahon and Patuzzi, 2002; Patuzzi et al., 2004). We found that noradrenaline in the superior olivary complex could evoke both excitatory and inhibitory effects on cochlear neural output, which were most likely due to excitation of lateral and medial olivocochlear neurons, respectively.

2. Materials and methods

2.1. Animals and anaesthesia

Nine pigmented guinea pigs of either sex weighing between 330 and 420 g were used. Experimental protocols conformed to the Code of Practice of the National Health and Medical Research Council of Australia and were approved by the Animal Ethics Committee of the University of Western Australia. Following a subcutaneous injection with atropine sulphate (0.65 mg/kg), guinea pigs were anaesthetised with 30 mg/kg Nembutal (sodium pentobarbitone) intraperitoneally and 0.15 ml Hypnorm (fentanyl citrate and fluanisone) intramuscularly. Adequate anaesthesia was maintained by an identical dose of Hypnorm every hour and a half dose of Nembutal every two hours. Paralysis was induced by an intramuscular injection of 0.1 ml of pancuronium bromide (2 mg/ml). Heart rate was monitored by ECG recording and did not increase after paralysis.

2.2. Surgical procedures

Animals were tracheotomised and artificially ventilated on carbogen (95% O_2 and 5% CO_2). Body temperature was maintained between 37.5 and 38 °C by a rectal probe connected to a thermostatically controlled heating pad. Animals were mounted between hollow earbars, the cochlea was exposed and an insulated silver recording wire was placed on the round window. Pure tones were delivered by a closed sound system. Custom written software (courtesy of G. O'Beirne and R. Patuzzi, written using LabVIEW, v 7.0; National Instruments Corp., TX, USA) was used to deliver tone stimuli and enabled automated and rapidly interleaved measurements of:

(1) The compound action potential (CAP) thresholds and amplitudes elicited by supra-threshold stimuli at seven different frequencies.
(2) Spectrum of the spontaneous neural noise.

For determination of CAP threshold the stimulus attenuation was adjusted to maintain a constant correlation level of 25% between successive averaged ($n = 7$) CAP waveforms (Patuzzi and O'Beirne, 1999). This measure provided acceptably stable threshold estimates with standard deviations typically around 1.5 dB, that were shown by extrapolation to be around 5 dB higher than the stimulus level that gave a correlation of zero (G. O'Beirne, unpublished results).

To assess the effect of noradrenaline injection, we measured amplitudes of the CAP 15 dB above threshold. Every measurement cycle of the software (approximately 55 s) provided us with 10 averaged ($n = 7$) measurements of the CAP amplitude at the selected frequencies (2, 4, 6, 10, 14, 18 and 22 kHz). For analysis every five measurements of the CAP amplitude were averaged, plotted over time and normalised. Some of the data showed a gradual small decline (drift) of the CAP amplitudes over the whole course of the experiment (up to 70 min), that was very different from the more rapid