Journal of Neuroscience Methods 273 (2016) 40–54

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Multichannel cochlear implant for selective neuronal activation and chronic use in the free-moving Mongolian gerbil

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HIGHLIGHTS

- First study to describe a multichannel CI for chronic use in the Mongolian gerbil.
- Selective and tonotopic neuronal activation was evident in auditory cortex.
- Impedances and EABR thresholds were stable over weeks after implantation.
- Chronic electrical stimulation was safe and effective in the free-moving gerbil.

ARTICLE INFO

Article history:
Received 31 May 2016
Received in revised form 5 August 2016
Accepted 8 August 2016
Available online 9 August 2016

Keywords:
Mongolian gerbil
Multichannel cochlear implant
Deafness
Chronic electric stimulation
Auditory cortex
Tonotopy
Channel selectivity
Impedance
Evoked auditory brainstem responses

ABSTRACT

Background: Animal models for chronic multichannel cochlear implant stimulation and selective neuronal activation contribute to a better understanding of auditory signal processing and central neural plasticity.
New method: This paper describes the design and surgical implantation of a multichannel cochlear implant (CI) system for chronic use in the free-moving gerbil. For chronic stimulation, adult-deafened gerbils were connected to a multichannel commutator that allowed low resistance cable rotation and stable electric connectivity to the current source.
Results: Despite the small scale of the gerbil cochlea and auditory brain regions, final electrophysiological mapping experiments revealed selective and tonotopically organized neuronal activation in the auditory cortex. Contact impedances and electrically evoked auditory brainstem responses were stable over several weeks demonstrating the long-term integrity of the implant and the efficacy of the stimulation.
Comparison with existing methods: Most animal models on multichannel signal processing and stimulation-induced plasticity are limited to larger animals such as ferrets, cats and primates. Multichannel CI stimulation in the free-moving rodent and evidence for selective neuronal activation in gerbil auditory cortex have not been previously reported.
Conclusions: Overall, our results show that the gerbil is a robust rodent model for selective and tonotopically organized multichannel CI stimulation. We anticipate that this model provides a useful tool to develop and test both passive stimulation and behavioral training strategies for plastic reorganization and restoration of degraded unilateral and bilateral central auditory signal processing in the hearing impaired and deaf central auditory system.

1. Introduction

To date, the cochlear implant (CI) is the most successful neural prosthesis with respect to the cumulative number of implantations in humans (>300.000) (Wilson and Dorman, 2008). Importantly, speech discrimination performance in CI subjects is dependent on the functional independence of stimulation sites or channels and, thus, the selective activation of neural populations in the auditory pathway (e.g., Chatterjee and Shannon, 1998; Henry et al., 2000; Throckmorton and Collins, 1999; Zwolan et al., 1997). Although contemporary CI systems provide between 12 and 22 electrical contacts, present speech-processors only activate 4–8 of these contacts as independent stimulation channels (e.g., Fishman et al., 1997; Friesen et al., 2001; Garnham et al., 2002; Kiefer et al., 2000; Lawson et al., 1996). The reasons for the limited number of activated channels are (1) extensive overlaps in the electric fields from different

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http://dx.doi.org/10.1016/j.jneumeth.2016.08.006
0165-0270/

contacts at the excited neurons (e.g., Fu and Nogaki, 2005), (2) temporal integration, masking or refractory effects in the auditory systems by the high stimulus rate [>1000 pulses per second (pps)] of current speech processing strategies and (3) deafness induced degradations in the periphery and in the spatial representation of electrical signals in the central auditory system (e.g., Raggio and Schreiner, 1999; Vollmer et al., 2007).

Improvements in the performance of CI subjects are thought to be correlated with an increase in the number of functional channels (Wilson and Dorman, 2008). There are multiple attempts to overcome the limited number of functionally independent channels: positioning of stimulation electrodes near to or inside the modiolus (e.g., Middlebrooks and Snyder, 2007, 2008); intracochlear optical stimulation of the auditory nerve (e.g., Jeschke and Moser, 2015; Richter et al., 2008); inducing the growth of neurites toward electrodes inside the scala tympani (e.g., Glueckert et al., 2008); focusing electrical current (e.g., Bierer et al., 2010, 2015) and generating "virtual sites" of intracochlear stimulation (Bonham and Litvak, 2008), and identifying mechanisms of temporal processing in the central auditory system in order to adapt speech-processing strategies. Animal models of multichannel CI provide an important basis for studying both the limitations and potential benefits of these approaches.

Multichannel CIs have been used in a variety of species, including guinea pigs (e.g., Landry et al., 2011; Snyder et al., 2004), ferrets (e.g., Hartley et al., 2010), cats (e.g., Coco et al., 2007; Fallon et al., 2009; Hartmann et al., 1997; Leake et al., 2013; Raggio and Schreiner, 1994; Ryugo et al., 2010; Schoenecker et al., 2012; Shepherd et al., 2011) and primates (e.g., Johnson et al., 2012; Xue and Pfingst, 1989). In small rodents, such as mice (Irving et al., 2013; Mistry et al., 2014), rats (Lu et al., 2005) and gerbils (Hessel et al., 1997; Kadner and Scheich, 2000; Wang and Scheich, 2001), only CIs with a maximum of three contacts have been studied, with the exception of acute experiments with thin-film stimulation electrodes in rats (Allitt et al., 2015, 2012). In contrast to the classical silicone based CI, thin-film electrode arrays offer higher contact density and deeper insertion, but reveal greater distance between electrode and modiolus (Allitt et al., 2015, 2012; Van Beek-King et al., 2014). Despite anatomical advantages, research in larger animals such as ferrets, cats and primates is time-consuming because of their slow development and aging, requires higher costs and effort in housing and breeding, and is ethically subordinate to the use of rodents. It is therefore advantageous to have access to multichannel CI models in smaller animals.

Moreover, it is known that auditory deprivation can induce profound changes in central neural processing of auditory signals. Successful deafening of animals depends on the species, applied method and age. To explore whether normal central neuronal processing and selective signal representation can be maintained or recovered by restoring auditory input, it is necessary to design a multichannel CI research system that is applicable for chronic use.

Here, we have developed a multichannel CI system that allows selective and tonotopically organized neuronal activation in auditory cortex of the free-moving adult deafened gerbil. The Mongolian gerbil (Meriones unguiculatus) is a well-established animal model for auditory research (for review: Budinger and Klump, 2008). In contrast to mice and rats that are also frequently used in auditory research, the hearing range of gerbils is similar to that of humans (Gleich, 2012; Ryan, 1976) and covers low frequencies <2 kHz. This makes the gerbil a suitable model for studying binaural processing of interaural time differences in both acoustic and electric hearing (Belliveau et al., 2014; Laumen et al., 2016; Maier et al., 2008; Pecka et al., 2010; Vollmer et al., 2014). Further, the gerbil is robust to surgery and anesthesia, and the large bulla and thin skull enable easy experimental access to the cochlea and cortical brain structures (Wang and Scheich, 2001). Contrary to mice and rats, the stapedial artery does not impede access to the round window, thus, reducing surgical risks of bleeding during CI insertion. Other advantages are the high reproduction rate, rapid development and easy breeding and handling. Gerbils can also be trained in even complex behavioral tasks (Hamann et al., 2002; Ohl et al., 2001; Wetzel et al., 2008). Moreover, in contrast to other rodents with good low frequency hearing (guinea pig, chinchilla) the gerbil is born deaf and has a late onset of natural hearing around postnatal day 12 (Harris and Dallos, 1984). It is possible, therefore, to deafen a gerbil before hearing onset (Hessel et al., 1998). As a result, the gerbil can serve as an animal model for prelingual deafness and cochlear implantation in children, and its entire hearing history can be controlled throughout life. However, selective and tonotopic central-neuronal activation by multichannel CI stimulation in a chronic preparation has not been reported in the gerbil.

We describe the design of a multichannel CI system for chronic use in the free-moving gerbil. Our findings confirm that cochlear implantation and chronic electric stimulation with the described system were stable and effective over several weeks. Acute electrophysiological mapping experiments revealed selective and tonotopically organized activation of neurons in gerbil auditory cortex (AC). Thus, the described CI system provides an important tool to (1) explore central-neuronal channel representation and interactions in a rodent animal model, (2) test for deafness- and stimulation-induced long-term functional and structural plasticity in the deaf central auditory system, and (3) conduct behavioral studies in the free-moving cochlear implanted gerbil.

2. Methods

2.1. Animals

All experiments were approved in accordance with the German law on the protection of animals and the directive of the European parliament and of the council of 22. September 2010 (2010/63/EU). A total of twenty-nine young adult gerbils were included in this study. Animals were separated into two experimental groups. Thirteen of these animals (age at implantation 89 ± 13 d) were deafened unilaterally, received a multichannel CI on the left side and were studied acutely (acutely-deaf unstimulated, 'AD' group). Normal hearing was maintained on the contralateral right ear. This allowed direct comparison of the spectral representation of responses to acoustic and multichannel electric stimulation in the AC of the same animal ($N = 6$).

The remaining 16 animals (age at implantation 66 ± 6 d; chronically-stimulated, 'CS' group) were deafened bilaterally and received a CI on the left side. After a recovery period of ~1 week (median 7 d, range 6–9 d), chronic intracochlear electric stimulation was initiated and continued over a period of four weeks. During the period of chronic stimulation, electrically evoked auditory brainstem responses (EABR) and electrode contact impedances were regularly assessed. This allowed us to monitor the long-term stability of the implant and the efficacy of chronic electric stimulation. In these chronically stimulated animals, also the effects of chronic electric stimulation on functional plasticity in central neural response properties were evaluated. These results will be summarized in a separate report.

2.2. Anesthesia

All recording and surgical procedures were conducted under general anesthesia. Animals were initially sedated by intraperitoneal injection [7.5 μl/g bodyweight (BW)] of a mixture of ketamine (7.5 mg/ml), xylazine (1.3 mg/ml), glucose (16.1 mg/ml) and NaCl (48.4 mg/ml). For short procedures (e.g., ABR record-