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卡那霉素致聋豚鼠耳蜗电极植入模型的建立及意义 *

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摘要 目的:探讨人工耳蜗电极的插入对耳蜗功能的影响,为研究人工耳蜗植入建立相应的动物模型。**方法:**取听力正常的豚鼠 8 只,4 只注射卡那霉素联合呋塞米致聋,为致聋组;4 只仅注射生理盐水,为对照组。对两组动物行听性脑干反应(ABR)及耳声发射(DPOAE)检查后,将耳蜗电极植入左侧耳蜗。**结果:**致聋组术侧 4 个频率段 ABR 阈移随着时间的推移逐渐减小,术后 24 h、48 h、72 h 时间段比较无显著性差异($P > 0.05$);对照组术侧 ABR 阈移随着时间的推移逐渐减小,32 kHz 频率的三个时间段比较有显著性差异($P < 0.05$),其余 3 个频率无显著性差异。此外,致聋组与对照组术侧耳 ABR 阈移比较均无显著性差异($P > 0.05$)。致聋组术前 5 个频率的 DPOAE 无法引出,术后 DPOAE 仍无法引出;对照组术前 DPOAE 均可引出,术后术侧的 DPOAE 均无法引出。术后 72 h 可见电极周围有组织包绕,固定良好,局部未见明显炎症反应。**结论:**本实验成功建立了卡那霉素致聋的豚鼠耳蜗电极植入模型,可为人工耳蜗植入术后颞骨病理改变的研究提供实验基础。

关键词:耳蜗;人工耳蜗;电极植入;豚鼠;卡那霉素
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Establishment of Cochlear Electrode Implantation in a Deaf Guinea Pig Model by Kanamycin *

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ABSTRACT Objective: To investigate the impacts of cochlear implant (CI) electrode on cochlear function in a guinea pig model, and provide reliable animal model for cochlear implant research. **Methods:** Eight guinea pigs with normal hearing were selected, four guinea pigs were administered with a single dose of kanamycin followed by furosemide to establish deaf group, while the other four were administered with saline as control group. After ABR and DPOAE tests, the eight animals underwent electrode-insertion surgery on their left ears. **Results:** In deaf group, ABR threshold shifts in the frequency range 4, 8, 16, and 32 kHz on the operative sides were gradually decreased with time, and the differences among the 24 h, 48 h and 72 h were statistically insignificant ($P > 0.05$). In control group, ABR threshold shifts in these frequency range on the operative side were gradually decreased with time as well, and the differences among the 24 h, 48 h and 72 h were statistically significant only in 32 kHz ($P < 0.05$). In deaf group, the DPOAE could not be elicited before and after the surgery; in control group, the DPOAE could be elicited before the surgery, but absent after the surgery. 72 h after the surgery, the electrodes were surrounded with tissue and fixed well, and no inflammatory response was observed. **Conclusion:** A guinea pig cochlear electrode implantation model with kanamycin-induced deafness was successfully established, which could provide experimental basis for the study of temporal bone pathological changes after cochlear implantation.

Key words: Cochlea; Cochlear implant; Electrode insertion; Kanamycin
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前言

人工耳蜗(cochlear implant,CI)是人类对听觉系统的最重要发明之一，截止到 2012 年底有超过 32 万耳聋病人接受 CI 手术[1]。CI 的基本原理是通过声音电信号转换装置将声能转化为电能,经植入电极将电信号传入耳蜗,从而绕过受损的内耳毛细胞,直接刺激听觉末梢产生听觉[2]。随着 CI 手术广泛应用于临床,术中及术后的并发症也逐年增加。既往研究提示 CI 术后电极对耳蜗可以产生相应的病理损伤,尤其是电极的插入性损伤[3]。为了达到更好的 CI 手术效果,术中选择合适的电极植入方式十分重要，由于很难在病人身上进行 CI 手术的相关研究,动物模型可以更好的模拟人类,从而促进 CI 手术不断完善[4]。不同的动物模型被成功应用于 CI 手术[5-8],其中豚鼠因其听觉系统发达,且耳蜗结构与人相似,是理想的实验动物[9]。因此,

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本研究选用豚鼠耳蜗为实验对象，通过卡那霉素联合呋塞米致聋豚鼠，采用直径较小的人工耳蜗电极在全麻下进行 CI 电极植入术，术中观察豚鼠的生命体征，术后观察豚鼠听觉功能改变及局部组织对电极的反应，旨在为研究 CI 电极植入后对耳蜗损伤的研究提供理想的动物模型。

1 材料与方法

1.1 实验动物及主要器材

健康成年且听力正常的豚鼠 8 只，体重 0.8-1.1 kg，雌雄各半，由西安交通大学实验动物中心提供，饲养于隔音的实验动物房，操作遵守西安交通大学医学部动物使用规定。主要器材为 Smart EP&OAE 听觉诱发电位 - 耳声发射记录系统(美国智听公司)，耳科显微镜(日本奥林巴斯公司)。

1.2 卡那霉素联合呋塞米致聋模型的建立

豚鼠根据随机数字表法进行分组：致聋组动物 4 只，按 1 g/kg 剂量皮下注射硫酸卡那霉素(美国西格玛公司)，40 min 后按 0.4 g/kg 剂量于腹腔注射呋塞米(中国科伦制药)，注射 3 d 后 ABR 检测 4、8、16、24 kHz 频率的阈值稳定在 55-80 dB 即为致聋造模成功；其余 4 只对照组豚鼠给予等剂量生理盐水皮下及腹腔注射[10]。

1.3 听觉功能检查

包括听觉脑干反应(auditory brainstem response，ABR)及畸变产物耳声发射 (distortion-product otoacoustic emission，DPOAE)。本研究中所有的豚鼠实验前均行 ABR 及 DPOAE 检测已排除听觉异常的动物。致聋组与对照组在术前及术后 24 h、48 h 及 72 h 在隔音室内行 ABR 及 DPOAE 检测以了解其听觉功能改变。测试时按 400 mg/kg 于豚鼠腹腔注射 10 %水合氯醛合剂，待麻醉成功后，采用听觉诱发电位 - 耳声发射记录仪检测。ABR 主要步骤：记录电极置于颅骨定点正中，略插入骨缝中但勿插入过深损伤脑组织，参考电极置于测试耳乳突部皮下，接地电极置于大腿皮下。选取频率为 4、8、16、32 kHz 的短纯音(tune burst)刺激声，强度从 90 dB 开始，逐渐递减，以反复出现 2 次以上 III 波的最低刺激强度定义为阈值[11]。DPOAE 主要步骤：将探头置于测试耳外耳道口，取 8、10、12、14、16kHz 作为测试频率，检出标准以 DPOAE 大于本底噪音 3 dB[12]。见图 1 AB。

1.4 手术方法

动物麻醉前禁食 12 h，经腹腔注射 10 %水合氯醛进行全身麻醉。麻醉后将动物右侧卧于恒温手术台，在无菌条件下行 CI 电极植入，局部备皮后采用左侧耳后切口，分离皮下及肌肉组织暴露出听泡，高速切割电钻在听泡的后部开孔，暴露圆窗，用尖针(直径 < 0.3 mm)于靠近圆窗后下方的耳蜗底转开窗，后用磨钻将开窗处扩大至电极直径大小(约 1 mm)，并小心将电极朝前下方插入进入鼓阶，插入后用肌肉填塞耳蜗开窗处，逐层缝合[13]。见图 2 A-C。

1.5 统计学分析

实验数据应用 SAS 9.4 统计软件进行分析，计算各组的均数± 标准差，各组阈移比较采用 t 检验，组内各时间段比较采用方差分析，以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 动物手术情况

豚鼠全麻后呼吸平顺，心跳规则，未观察到特殊不适。电极植入过程中豚鼠生命体征平稳，局部出血少，术后麻醉苏醒良好。于术后 72 h 打开伤口，可见电极固定良好，开窗处局部组织愈合好，无明显炎症反应。随后处死动物，取出耳蜗，可观察到电极成功插入耳蜗鼓阶，耳蜗开窗损伤较小，局部未观察到较重的炎症及异物排斥反应。见图 2 D-F。

2.2 CI 术对豚鼠 ABR 阈值的影响

致聋组术后 24 h 行 ABR 检测，4、8、16、32 kHz 4 个频率术侧 ABR 阈移均增大，48 h 后 ABR 阈移较之前减小，72 h 后 ABR 阈移略减小，三个时间段阈移比较无显著性差异 ($P > 0.05$，图 3)；对照组术后 24 h 行 ABR 检测，术侧 ABR 阈移显著增大，48 h 后 ABR 阈移较之前减小，72 h 后 ABR 阈移略减小，32 kHz 频率三个时间段阈移比较有显著性差异($P < 0.05$)，其余 3 个频率无显著性差异；4、8、16、32 kHz 4 个频率术侧耳致聋组的阈移平均值均小于对照组，但两组之间的差异不显著 ($P > 0.05$)。见图 3。

2.3 CI 术对豚鼠 DPOAE 的影响

致聋组术前 8、10、12、14、16 kHz 频率的 DPOAE 无法引出，术后 24 h、48 h、72 h 的 DPOAE 仍无法引出；对照组术前 8、10、12、14、16 kHz 频率的 DPOAE 均可引出，术后术侧耳的 DPOAE 均无法引出。

3 讨论

图 1 豚鼠的听性脑干反应检查及植入电极注：A: 听性脑干反应(ABR)电极的位置；B: ABR 检测中的波形，其中 III 波最明显；C: 豚鼠耳蜗植入电极(直径约 1 mm)

Fig. 1 Auditory brainstem response test and the implanted electrode for guinea pigNote: A: The position of the electrodes in auditory brainstem response (ABR)；B: The waveforms in ABR, in which the III wave is the most obvious one；C: The implanted electrode in the guinea pig model (Diameter approximately 1 mm)

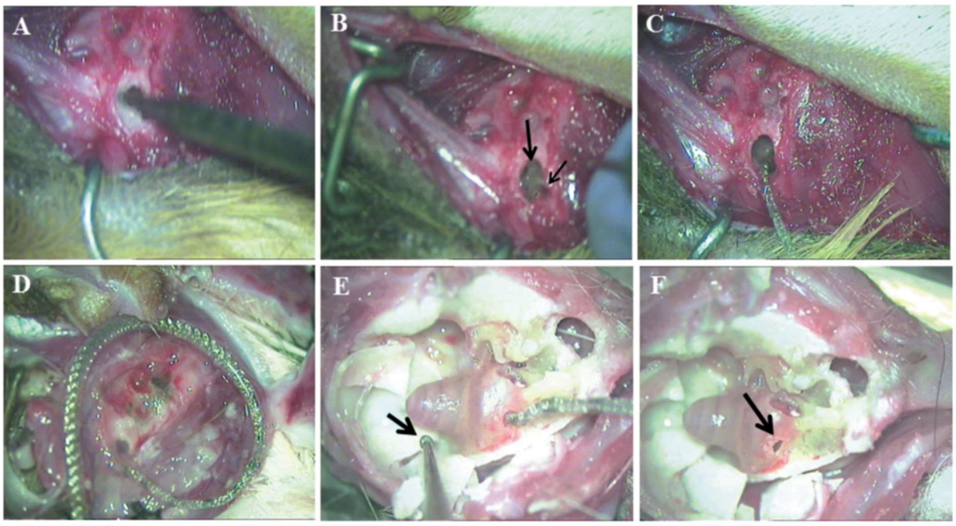

图 2 豚鼠耳蜗电极植入术中及术后情况注：A: 高速切割钻磨开听泡；B: 打开听泡后暴露圆窗(粗箭头)，并于圆窗后下方耳蜗底转开窗(细箭头)；C: 将电极沿前下方向插入开窗处，进入鼓阶；D: 术后 72 h 打开切口，可见周围组织包绕电极，无明显炎症反应及异物反应；E: 取出耳蜗后，可见电极成功插入耳蜗，所用磨钻直径与电极直径相近(箭头)；F: 可见开窗处未见明显炎症。

Fig. 2 Intraoperative and postoperative phases of cochlear implant in guinea pigNote: A: The otic bulb was opened by a high-speed drill; B: The round window was observed, and the basal turn of the cochlea was opened (Bold Arrow); C:Insert the electrode into the opening of the cochlea and further into the scala tympani; D: The operative incision was opened 72 h after the surgery, and no inflammatory response as well as foreign body reaction were observed; E: After dissecting the cochlea, we found the electrode was in proper position in the cochlea, the diameter of the drill was similar with the diameter of the electrode (Arrow) ;F: No inflammatory response was observed near the opening of the basal turn.

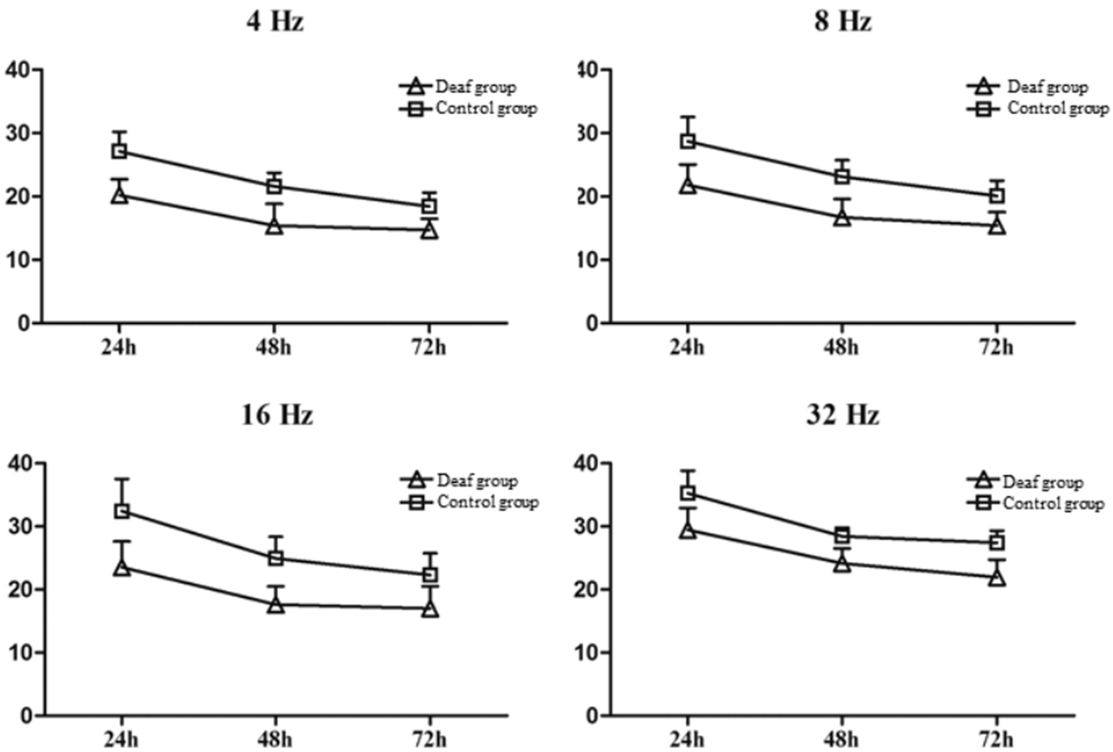

图 3 人工耳蜗电极植入后 ABR 的阈移注：依次为术侧 4、8、16 及 32 kHz 频率段 ABR 的阈移，各个频率段 ABR 阈移随着时间的推移逐渐减小；图中横轴为术后时间，纵轴为 ABR 阈移 (均值± 标准差，dB)

Fig. 3 ABR threshold shift after cochlear implant

Note: ABR threshold shift in the frequency range 4, 8, 16, and 32 kHz on the operative side, and the ABR threshold shifts were gradually decreased with time in all the frequency ranges; the horizontal axis showed the postoperative time, and the vertical axis showed ABR threshold shift (mean± SD, dB)

豚鼠由于易养殖、来源广、与人类听觉系统较为相似等特点被广泛应用于耳科学的研究[14-16]。此外，大鼠、猫及猴子也被应用于人工耳蜗植入模型。然而，与豚鼠相比，大鼠的耳蜗相比较小，手术过程中面神经表浅易受损伤，此外大鼠需要直径更细的电极。猫和猴子虽然耳蜗较大，但其体型较大难于饲养且实验成本较高。卡那霉素是一类重要的氨基糖苷类抗生素，氨

基糖苷类抗生素耳毒性大，且损伤不可逆，是药物性聋的主要病因。既往的实验表明，卡那霉素联合呋塞米可以有更强的致聋作用，联合用药不仅可以损伤小鼠耳蜗的毛细胞，同时可以促使螺旋神经节细胞的退化变性[17]。最后，为使电极顺利插入耳蜗，我们选取直径较小(1 mm)的电极进行插入，尽量减少插入过程中带来的插入性损伤。既往研究通过 ABR 和 DPOAE 相结合以反映动物的听觉功能。ABR 可以检测听觉传入神经通路的功能，其波形主要由 I、II、III、IV、V 波组成，依次分别来源来源于耳蜗神经、耳蜗核、上橄榄核、外侧丘系核、下丘核，其中因 III 波振幅较大易观测，从而作为 ABR 检测的指标[18-22]。DPOAE 可以检测耳蜗外毛细胞的功能状态，其是由声音刺激耳蜗后，在外耳道记录到的声音能量[23-27]。本实验中，致聋组及对照组术后 72h 的 ABR 阈移基本在 20 dB 左右，证明电极的插入对耳蜗功能影响较小。然而，在术后 24 h 时 ABR 阈移较大，随着时间的推移均逐渐减小，其原因可能是由于电极插入造成的耳蜗急性损伤随着组织的愈合逐渐减小。此外，对照组的 ABR 阈移均值高于致聋组的阈移，但两者差异统计学分析上不显著，对此可能的原因是致聋组的毛细胞已经破坏，而对照组术前毛细胞的功能正常，电极插入的过程中会部分影响到毛细胞。由于术前致聋组的毛细胞已经被卡那霉素破坏，因此致聋组术后无法引出 DPOAE。然而，对照组术前毛细胞功能正常，DPOAE 均能引出，而术后均不能引出，原因可能是电极对耳蜗基底膜造成的损伤所致。虽然术中我们尽量小心避免电极对耳蜗的损伤，但耳蜗开窗手术无法彻底避免插入性损伤。为了解决这个问题，我们在术中尝试圆窗入路植入耳蜗电极，但由于豚鼠圆窗开口向前下，此处有骨质阻挡，难以插入，见图 2 B 中粗黑箭头。我们将在随后的实验中在组织学水平研究如何最低程度的减少此种损伤。总之，本实验成功建立了卡那霉素致聋的豚鼠耳蜗电极植入模型，动物耐受良好，术后解剖可见电极成功植入耳蜗鼓阶，开窗处局部组织愈合良好，无明显炎症及异物反应，此模型的建立可为人工耳蜗植入术后颞骨病理改变的研究提供实验基础。

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