Controlled Infusion for Drug Delivery to the Inner Ear in Guinea Pigs over Extended Periods

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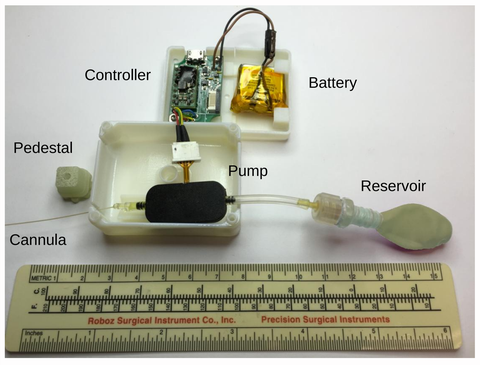
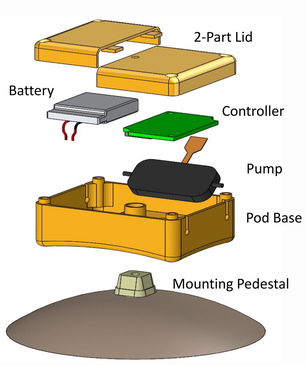
Introduction

We have created a wearable infuse-only device capable of drug delivery to the inner ear of guinea pigs for extended periods of time. The device is easily fabricated from commercially available components. While this simple, infusion-only system does not have the capabilities or the advantages of the reciprocating system we have developed (see poster 592), it will serve some basic needs for controlled delivery of agents into the inner ear of animals.

Engineering

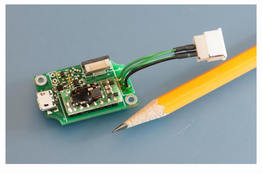
The device comprised a piezoelectric pump, programmable controller, battery, elastic reservoir, and infusion cannula. The entire assembly is mounted to a the head of the guinea pig for chronic delivery with the untethered device.



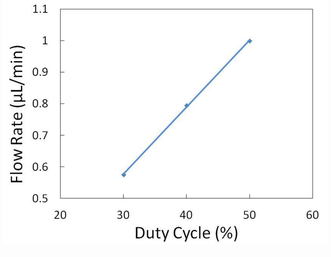


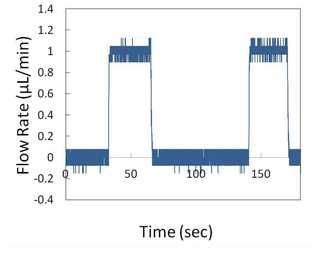
Overview A commercial miniature piezoelectric pump (Bartels Mikrotechnik mp6) was operated by our custom, programmable drive circuit and powered by a lightweight rechargeable 250mA·hr lithium polymer battery (Tenergy 062025). The reservoir was adapted from a conventional latex rubber balloon. The components were fit into a 3-D printed housing that attached to a skull-mounted fiberglass pedestal. The infusion cannula consisted of 21 cm of polyetheretherketone (PEEK) capillary tubing, with a 11-mm segment (201 μm OD, 101 μm ID) of fluoropolymer capillary (Zeus Plastics) at the distal end. The long capillary provided hydraulic resistance to reduce the flow rate to desired levels, as discussed below.

We programmed the controller to periodically cycle the pump with "on" times of seconds to minutes at intervals of 5 min or 30 min. The instantaneous flow rates were 0.5—1 μL/min depending on pump settings, pulse volumes were 1—2 μL per cycle, and the resulting cumulative infusion rates were 1—12 μL/hr.



Two different pump controllers were developed as the form factor of the pod evolved over time: Both systems used a microcontroller to time signals to a pre-assembled pump driver circuit manufactured specifically for the pump (mp6 OEM Controller, Bartels Mikrotechnik). This driver receives logic level input which enables the high voltage output (up to 250 Vpp) at frequencies of 30—200 Hz delivered to the piezoelectric diaphragms in the pump. The pump flow rate was determined by these settings. Board #1 used a PIC microcontroller programmed via external hardware with 2 dynamically selectable operating modes. Board #2 (shown above) was fully programmable via USB interface.

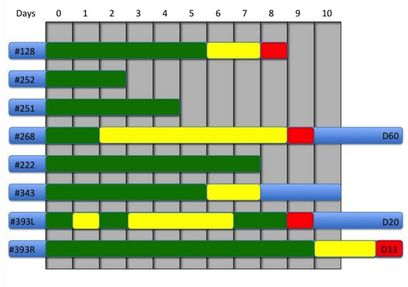




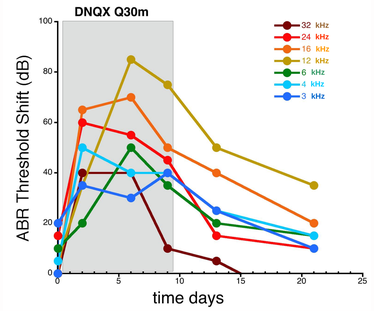
Very low flow rates with the Bartels pump were achieved by increasing the fluid resistance at the outlet. With no load pressure, the minimum flow rate of the Bartels pump is about 20 μL/min. We achieved lower rates by increasing resistance to the outflow cannula with a 22-cm length of 50-μm ID PEEK tubing. The flow rate was further adjusted by varying the duty cycle of the 39 Hz output to the pump diaphragms.

In Vivo Assessment of Pump

We have infused drugs into the inner ear at variable flow rates for periods of 2 to 9 days. Bars in green indicate when the pump was working, as verified by pharmacology or direct observation. Bars indicated in red are days when flow was known to have stopped. Bars in yellow indicate periods when we did not have confirmation of pump performance.

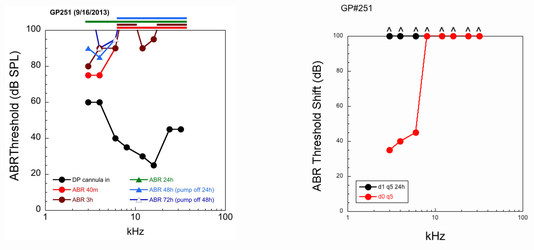


Stable concentrations of drug in the cochlea could be achieved for over a week. Threshold shifts are plotted for different CF regions as a function of days. DNQX, a neurotransmitter receptor blocker that can attenuate neural responses, was perfused over the period indicated with gray shading. ABR threshold shifts were relatively constant for the 9 days over which DNQX was infused. Effects were similar in all frequency regions of the cochlea, though largest near the tip of infusion cannula (12- 16 kHz) and smallest near the cochlear aqueduct (32kHz).



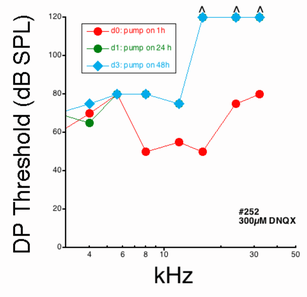
The magnitude of the effects of DNQX could be controlled by modifying the concentration of the drug and the frequency at which it was delivered. The effects shown here were obtained by delivering 1 mM of DNQX at 0.5 μl/m for 2 m every 30m. Larger effects of DNQX were achieved more rapidly when drug was delivered more frequently (e.g. every 5 m) even when lower concentrations (0.3 mM) were used.

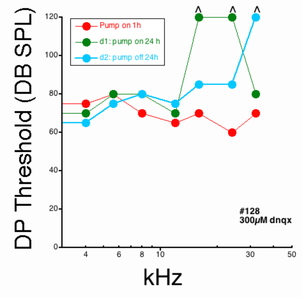
With acute (hours) delivery of DNQX, effects were largely confined to the frequency regions bathed by the drug (12 to 32 kHz). By 24h, DNQX effects were apparent throughout the cochlea. Infusion of a glutamate receptor blocker, DNQX, allowed us to assess both the spatial distribution of the drug (via frequency-specific CAPs and the nonspecific effects (i.e changes in DPOAEs) of the delivery technique.



The left plot indicates ABR threshold as a function of stimulus frequency; the plot on the right indicates threshold shifts at 40 min (red) vs 24 h (black)

DPOAE Thresholds in High CF regions were reversibly elevated with long-term infusion. After 24h or more of infusion, we observed a reversible elevation of DP thresholds at high (16-32 kHz) regions. This corresponds to frequency regions between the tip of the cannula and the cochlear aqueduct. DP threshold shifts were observed with infusion of artificial perilymph, but not when the cannula was in place without flow. Shifts occurred more rapidly when the inner ear was infused every 5 m compared to every 30m.

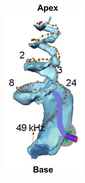




Surgery and Methods

Surgery was performed under fentanyl/haloperidol/pentobarbital anesthesia. A bullectomy was made behind the ear. A cochleostomy was placed approximately 0.5 mm distal to the round window and PTFE tubing inserted apically into the scala tympani to a length of 3 mm. A small amount of dental cement was used to seal the cochleostomy around the tubing to prevent perilymph leakage.

Hearing measurement: Distortion product otoacoustic emissions (DPOAEs) and compound action potentials (CAPs) or auditory brainstem responses (ABRs) were measured at 2.78, 4, 5.6, 8, 12, 16, 24, and 32 kHz. The CAP electrode was placed next to the round window niche and fixed in place. Hearing was measured before and after cannula insertion and at several different time points after turning the pump on.



Discussion

Controlled drug delivery for extended periods into the scala tympani for animal experimentation has been demonstrated with a simple device constructed from commercially available components. The components are relatively inexpensive, allowing small laboratories with some electronics expertise to construct and use the device for inner ear drug delivery. We are happy to provide specifications for building and programming the device.

This work was made possible by NIH NIDCD Grant 5 R01 DC006848-08

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