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Combined ionic direct current and pulse frequency modulation improves the dynamic range of vestibular canal stimulation

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Abstract

BACKGROUND: Vestibular prostheses emulate normal vestibular function by electrically stimulating the semicircular canals using pulse frequency modulation (PFM). Spontaneous activity at the vestibular nerve may limit the dynamic range elicited by PFM. One proposed solution is the co-application of ionic direct current (iDC) to inhibit this spontaneous activity.

OBJECTIVE: We aimed to test the hypothesis that a tonic iDC baseline delivered in conjunction with PFM to the vestibular semicircular canals could improve the dynamic range of evoked eye responses.

METHODS: Gentamicin-treated chinchillas were implanted with microcatheter electrodes in the vestibular semicircular canals through which pulsatile and iDC current was delivered. PFM was used to modulate vestibulo-ocular reflex (VOR) once it was adapted to a preset iDC and pulse-frequency baseline. Responses to stimulation were assessed by recording the evoked VOR eye direction and velocity.

RESULTS: PFM produced VOR responses aligned to the stimulated canal. Introduction of an iDC baseline lead to a small but statistically significant increase in eye response velocity, without influencing the direction of eye rotation.

CONCLUSIONS: Tonic iDC baselines increase the dynamic range of encoding head velocity evoked by pulsatile stimulation, potentially via the inhibition of spontaneous activity in the vestibular nerve.

Keywords

Vestibular system; vestibular prosthesis; electrical stimulation; vestibulo-ocular reflex; neural implant; direct current

1. Introduction

Bilateral vestibulopathy (BVP) is a debilitating condition, characterized by loss of the vestibulo-ocular reflex (VOR), unstable gaze and oscillopsia, reduced dynamic visual acuity

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and impaired balance during standing and locomotion [19]. Patients suffering from severe BVP have greatly reduced independence and quality of life [10]. Rehabilitation therapy can effectively lessen the impact of BVP symptoms [20] but there remain no other treatment options for many of the underlying etiologies associated with BVP. One potential solution to restore vestibular sensation in patients affected with BVP is functional electrical stimulation of the surviving vestibular nerve using a vestibular prosthesis [6, 16]. Optimization of device efficacy remains an important avenue of preclinical research for the continued development of these vestibular prostheses [14].

The semicircular canals of the vestibular system encode direction of head rotation by modulating spike rate around a spontaneous spike rate baseline [13]. Ideally, vestibular prostheses replicate the full range of spike frequencies available to the vestibular nerve, but this approach is limited by remaining spontaneous activity which, although reduced, is not fully extinguished in animal models of BVP [11]. To overcome this limitation, the vestibular system is adapted to and then modulated around an artificially elevated pulse rate baseline. For example, the vestibular prostheses might pulse at a 100 PPS baseline ‘rate’ which would add entrained spikes to the preexisting spontaneous activity. Once the system adapts to the new combined artificial and spontaneous rate, it is possible to transiently lower the prosthesis stimulation rate to down-modulate activity in the nerve, although never completely to 0 as the preexisting spontaneous rate will remain. While this approach successfully elicits both directions of encoded head rotations, it has been suggested that this elevated baseline may fail to fully replicate the dynamic range of encodable head rotations in the normally functioning system leading to a widening of asymmetric responses between head rotations contralateral and ipsilateral to the implanted canals [5, 14].

Most neural prostheses including vestibular prostheses rely on biphasic charge-balanced pulses to stimulate the neural tissue [15]. It has previously been shown that the application of anodal direct current (DC) to the vestibular system can inhibit baseline activity in the vestibular nerve [9]. This approach could improve the function of vestibular prostheses by removing spontaneous activity at the nerve and thus allow for down-modulation to below spontaneous baseline rates. Unfortunately, chronic DC delivery is unsafe at the electrode/tissue interface as it inherently violates charge-injection criteria, creating toxic electrochemical byproducts [2, 17]. Progress on a novel implant design capable of safely delivering ionic direct current (iDC) while retaining charge balance at the metal-saline interface has provided an opportunity to explore the possibility of using DC improving the efficacy of vestibular prosthesis stimulation [7, 8]. We have recently demonstrated ability of iDC to modulate vestibular output [1]. The possibility that a similar improvement in efficacy could be achieved with pulse frequency modulation (PFM) paired with tonic inhibitory iDC delivery to remove the spontaneous baseline has not been explored. A combined iDC + PFM design would have the advantage of a simpler iDC delivery control system and can better utilize preexisting vestibular implant designs and expertise. In this study we investigate the potential for a combined iDC + PFM stimulation strategy to increase the dynamic range of reflexive eye rotations associated with vestibular system modulation.

2. Methods

2.1. Surgical techniques

Adult wild-type chinchillas were used for experiments in this study. All experimental protocols were approved by the Johns Hopkins Animal Care and Use Committee (Protocol #CH15M38). The surgical techniques used here are identical to those previously described in detail [1]. In brief, three animals were treated bilaterally with 0.5 mL intratympanic injections of 26.7 mg/mL gentamicin to emulate BVP [11]. One month after treatment, animals were placed under isoflurane anesthesia and the mastoid bullae exposed and opened using an otologic drill. Small windows were exposed in the left ear posterior and superior semi-circular canals and the common crus. Plastic microcatheter tubes (20 μ L microloader pipettes; Eppendorf, Hamburg, Germany) containing a physiological saline solution suspended in 5% agar (146.5 mM NaCl; 3.3 mM KCl; 1.3 mM CaCl₂; 0.9 mM MgCl₂ 0.7 mM NaH₂PO₄; 10 mM HEPES; pH 7.4) were inserted into these openings to deliver electrical stimulation. The setup was then secured using dental cement and a phenolic post affixed to the midline perpendicular to the skull to allow for head restraint during video oculography. Animals were then allowed to recover and monitored post-surgery for a period of at least 2 weeks before experiments were performed.

2.2. Eye movement recording

To assess the efficacy of electrical stimulation we used real-time, 3-dimensional video-oculography (3D VOG) to record eye movements associated with the vestibulo-ocular reflex (VOR). This system has been previously described in detail [1, 4, 5]. The left eye was topically anesthetized via application of proparacaine (5 mg/mL; Bausch & Lomb, Rochester, NY) and the pupil constricted via pilocarpine (10 mg/mL; Bausch & Lomb, Rochester, NY) eye drops. A marker consisting of three fluorescent yellow squares on a black film was placed on the cornea using veterinary tissue glue (VetOne, Boise, ID) and illuminated via four UV-emitting diodes. A USB3 Camera (FL3-U3- 13Y3M-C, Flea3 1.3 MP Mono USB3 Vision; Point Grey, BC, Canada) retrofitted with a 1/4" format, 16.0mm-focal length, f/2.0 C-mount board lens (BL160; Allthings Inc., Australia) was used to acquire 496 400 pixel, 8-bit gray-scale images at 200 Hz using custom software written in LabVIEW (National Instruments, Austin, TX). This system captures 2-dimensional movement of the illuminated eye marker and outputs 3-dimensional eye velocities corresponding to the axes of the three semicircular canals: horizontal (H), left anterior/right posterior (LARP), and right anterior/left posterior (RALP) [6].

2.3. Electrical modulation

To deliver iDC safely during an acute experiment we used a setup consisting of a precision current source (Keithley Model 6221 AC and DC Current Source; Tektronix, Beaverton, OR) connected to the animal via agar-gel microcatheter tubes implanted in the posterior and superior semicircular canals, with a tube in the common crus to act as a return [1, 8]. We positioned the metal interface (20-gauge steel needles) at the other end of the microcatheter tubes, far from the tissue. These tubes acted as a salt-bridge that could deliver ionic current while isolating toxic electrochemical biproducts from the tissue interface. Both iDC and pulsatile electrical current were delivered through the same electrodes to simplify the

surgery and prevent differences in placement between a tube vs lead wire from potentially confounding the results. To determine the maximal dynamic range of eye responses from a given iDC baseline, the semi-circular canals were stimulated individually using cathodic-first, charge-balanced biphasic pulses with a 200 μ s phase width and a 25 μ s interphase gap. Both the superior and posterior canals were tonically stimulated with a pulse frequency baseline of 60 PPS and a constant current anodic iDC ‘offset’ (with respect to the tube positioned in the common crus). Animals were considered ‘adapted’ to this baseline stimulation when the eye ceased to display nystagmus in response to the tonic stimulation. Figure 1 shows example pulse waveforms at a 100 μ A amplitude without iDC (A) and with a iDC baseline (B). iDC adaptation amplitude was randomized to prevent experimental sequence-imposed bias, across a range of 0 to +40 μ A in 10 μ A steps. Pulses were then modulated in each canal around the 60 PPS baseline down to 0 PPS and up to 420 PPS using 20 repetitions of trapezoid steps with a 25 ms ramp up, 75 ms plateau, 25 ms ramp down and an 875 ms inter-step period. Between trials we varied pulse amplitude from 50 μ A to 175 μ A in 25 μ A steps. We chose this range of pulse amplitudes as we found that lower amplitudes failed to produce a measurable response and higher amplitudes consistently elicited noxious activation of the facial nerve (as determined by facial twitch). We chose +0 to +40 μ A as our range for iDC baselines based on our previous experiments showing physiological responses within this range of iDC [1]. We chose 60 PPS as our adapted baseline and 0–420 PPS as our modulation steps because this mimics the physiological range of neural firing in the healthy chinchilla [12] and 60 PPS baselines produce an optimal dynamic range of VOR eye responses [4, 5].

2.4. Data analysis

Output of the 3D-VOG system was analyzed offline via software developed in LabVIEW and MATLAB (MathWorks, Natick, MA) [1, 6]. Eye rotation velocity in 3D was calculated from raw positional data interpolated on a 1 kHz time base and then filtered by a low pass filter and a running spline interpolation filter (LabVIEW “Cubic Spline Fit” module with balance parameter 0.99995). Eye movements associated with saccades, blinks, marker slippage or lid impact and were manually removed from the data analysis. Maximum peak eye velocity was determined by taking the median peak velocity in the axis of rotation corresponding to the stimulated semicircular canal across 10 step repetitions. We also investigated changes in the direction of eye rotation by calculating the angle of axis misalignment for each peak velocity, defined as the difference between the calculated vector of eye rotation and the ‘ideal’ rotation vector aligned to the axis of the stimulated semicircular canal. We define eye rotations consistent with an increased firing of the vestibular afferent (increased pulse frequency) as ‘excitatory’ and eye rotations consistent with a decreased firing of the vestibular afferent from the elevated baseline (decreased pulse frequency) as ‘inhibitory’. Statistical Analyses were performed using GraphPad Prism v.6 (San Diego, CA, USA). Results are expressed as the mean standard error of the mean (SEM). Differences in amplitude and angle of axis misalignment across pulse amplitude and iDC baseline were examined by paired *t*-test or two-way analysis of variance (2-way ANOVA). A Holm-Sidak *post hoc* test was used to determine significance for multiple pairwise comparisons. Details of individual tests are also provided in the results. In all figures, statistical significance is expressed as $P < 0.05$.

3. Results

To assess dynamic range of PFM-evoked VOR velocities with and without an anodic iDC baseline, we stimulated the left posterior canal in all three experimental animals and the left superior canal in two of these animals. Figure 2A shows a stimulus trace of pulse frequency modulation in spikes per second to give context for the following eye velocity traces. Figure 2B–C show representative traces of posterior canal trials at 100 μ A pulse amplitude without an iDC baseline (B) and with a +30 μ A iDC baseline (C). Lines indicate left eye rotational velocity about the axes of the three semi-circular canals; posterior/right anterior (LARP), left anterior/right posterior (RALP) and horizontal (Z). When pulse frequency was modulated up from the baseline to 420 PPS, the eye rotated in a direction consistent with an ‘excitatory’ up-modulation of the vestibular nerve in the stimulated canal (left posterior, black arrowheads). When pulse frequency was modulated down from baseline, the eye rotated in the opposite, ‘inhibitory’ direction, consistent with down-modulation of the vestibular nerve (grey arrow-heads).

We first analyzed maximal eye velocities achievable with and without iDC delivery. Figure 3 compares individual maximum average peak eye velocities achievable both without any iDC baseline for excitatory (3A) and inhibitory (3B) eye rotations. The horizontal line and bars indicate the population mean and standard error of the mean (SEM). Circles are VOR responses resulting from posterior canal stimulation and squares are responses from superior canal stimulation. Grey dotted lines link responses for the same stimulated canal. During electrode placement in one superior canal, we observed a response (sudden and rapid nystagmus) we associate with accidental surgical ablation of the superior canal cupula. The resultant responses to stimulation in this canal (marked with an asterisk) were clearly atypical. We treated these datapoints as outliers and did not include them in our statistical analysis but have included them here for discussion. Maximum eye velocity magnitudes were significantly larger with an iDC baseline for both excitatory eye rotations (Paired *t*-test; mean of differences = 102 ± 67 °/s; $P = 0.048$; $n = 4$ canals, 3 animals) and inhibitory eye rotations (Paired *t*-test; mean of differences = 19 ± 9 °/s; $P = 0.002$; $n = 4$ canals, 3 animals).

Having determined a maximal effect of iDC delivery on pulse frequency modulated VOR magnitudes in our sample, we then examined the population relationship between pulse amplitude, iDC baseline and peak eye velocity. Figure 4 shows peak eye velocity for excitatory (4A) and inhibitory (4B) eye rotations as a function of both pulse amplitude and iDC baseline amplitude. As pulse amplitude increased, both excitatory and inhibitory eye velocity increased (2-way ANOVA; $P < 0.001$; $n = 4$ canals, 3 animals). As iDC amplitude increased, eye velocity also increased (2-way ANOVA; $P = 0.023$ for excitatory; $P = 0.002$ for inhibitory; $n = 4$ canals, 3 animals). There was no interaction between iDC amplitude and pulse amplitude (2-way ANOVA; $P > 0.999$; $n = 4$ canals, 3 animals). Pairwise comparisons revealed a significant increase in excitatory eye velocity at +30 μ A iDC for excitatory eye rotations ((2-way ANOVA; $P = 0.048$; $n = 4$ canals, 3 animals) and at both +20 μ A and +30 μ A iDC for inhibitory eye rotations (2-way ANOVA; $P = 0.017$ at +20 μ A; $P = 0.008$ at +30 μ A; $n = 4$ canals, 3 animals) but not at +40 μ A in either condition (2-way ANOVA; $P > 0.9$; $n = 4$ canals, 3 animals). These results suggest that the increase in peak

eye velocity resulting from co-delivery of iDC and PFM is effective only within a range of iDC amplitudes.

We analyzed angle of axis misalignment to examine the possibility that an iDC baseline might also influence with the direction of eye rotation. If an increased rotational eye velocity was consistently paired with off-axis rotation this could confound any functional benefit provided by an iDC baseline. Figure 5 shows a box-and-whiskers plot of angle of axis misalignment for both excitatory and inhibitory eye rotations. There were no significant differences between pulse amplitudes or iDC baselines in any condition (2-way ANOVA; $P > 0.9$; $n = 4$ canals, 3 animals), so we grouped all datasets together to allow for simpler visualization. There was no significant difference in angle of axis misalignment between PFM controls and PFM + iDC baseline conditions for either excitatory or inhibitory eye rotations (2-way ANOVA; $P > 0.9$; $n = 4$ canals, 3 animals), suggesting that tonic iDC delivery did not influence the direction of eye rotation elicited via pulse frequency modulation.

4. Discussion

The dynamic range of reflexive eye responses associated with stimulation of the semicircular canals is thought to be limited by remaining spontaneous activity at the vestibular nerve [4, 14]. In this study we aimed to explore the hypothesis that by using an anodic DC baseline to suppress baseline activity it would be possible to increase the dynamic range of eye rotations in response to pulse frequency modulation. We found that a small but statistically significant increase in peak eye velocities could be achieved with the addition of an anodic baseline, and this increase did not come at the cost of misaligned eye rotation. These results are consistent with our hypothesis, but the magnitude of the effect was relatively small with an average 19 %/s or 38% increase in the inhibitory eye velocities. In comparison, our previous work assessing the feasibility of direct iDC amplitude modulation (rather than used solely as a suppressive ‘baseline’) has managed to improve inhibitory eye rotation velocities by 200% compared to PFM controls [1]. It is possible that the current experimental setup could be optimized to improve the benefit of this stimulation strategy. We achieved similar peak velocities in our controls to previous publications [1, 3, 4] and the stimulus space we explored appeared to achieve maximal responses for both PFM and DC amplitude before facial twitch or loss of the beneficial effect. These results suggest that we might expect any improvement from optimization of the current methodology might therefore be modest and thus is unlikely to be pragmatically useful towards an implantable iDC device for restoration of vestibular function. The development of a single-channel, tonic square wave, anodic only iDC delivery device would have been significantly simpler and faster than a multi-channel, arbitrary waveform, anodic + cathodic iDC delivery device that will be necessary for iDC only modulation. We thus believe it was still important to explore the possibility that combined modulation of iDC+PFM was a more effective vestibular stimulation technique than iDC to guide future development of iDC delivery in the vestibular system.

We decided to reject one set of superior canal trials due to a response post electrode implantation that strongly suggested an ablation of the superior canal cupula. Spontaneous activity in the vestibular afferent is generated by hair cells at the sensory interface [13]. We

thus might expect spontaneous activity to sharply drop in the afferent following ablation of the cupula. If the increase in dynamic range of eye velocities following iDC stimulation is indeed due to spontaneous activity suppression as we hypothesize, with no activity left to suppress, there would be no room for improvement in ablated canals. This is precisely the result we recorded in our outlier, with not only greatly reduced peak eye responses but also no noticeable increase in eye response amplitude with the introduction of iDC. This provides some further observational evidence that suggests our proposed mechanism for increased dynamic range in response to a tonic iDC baseline may be accurate. However, a proper validation of this proposed mechanism will only be possible following characterization via single unit recordings in the chinchilla vestibular afferent.

While the immediate effect of anodic DC on the vestibular nerve has previously been examined [8], the mechanisms involved in tonic iDC delivery and the interaction between pulsatile stimulation and an iDC offset have not. Our results could be used to generate testable hypotheses for single unit experiments using iDC and/or PFM stimulation of the vestibular canals. Specifically, we found that the improved dynamic range in our iDC baseline conditions was only evident within a relatively small iDC window (+20 to +30 μA) and was attenuated by +40 μA iDC. We propose two competing hypotheses that may explain this effect. Firstly, anodic iDC achieves suppression of neural activity by hyperpolarizing the cell membrane [18]. While this should suppress spontaneous activity as discussed in our hypothesis, it likely also increases the threshold for pulse amplitude stimulation (i.e. at higher amplitudes the pulse amplitude may not be sufficient to depolarize the iDC-hyperpolarized membrane to threshold in some neurons). Once the iDC has completely suppressed spontaneous activity in the afferent, we might thus expect further increases in anodic iDC amplitude to attenuate and then block the pulse-evoked response. Secondly, this effect could also be explained via an alternative hypothesis: anodic current alone can also generate spike firing via depolarization at the virtual cathode 'side lobes' [18]. With increased anodic iDC it is possible that we are blocking propagation of spontaneous activity generated at the hair cell, but then evoking new spontaneous activity at the virtual cathode. This would create baseline activity in the nerve that would eventually counteract the baseline activity reduction caused by the anodic hyperpolarization. We plan to test these hypotheses by recording single unit afferent activity during iDC and/or PFM stimulation. If the iDC is blocking pulsatile stimulation we might expect to see an increased threshold for pulse-elicited action potentials in the nerve. Alternatively, if spontaneous activity is being generated at the virtual cathode, we would instead see an increased spontaneous spike frequency with increasing iDC current.

4.1. Conclusions

Our results show that a tonic iDC baseline coupled with pulse frequency modulation in the semicircular canals results in a larger range of evocable reflexive eye rotations when compared to pulse frequency modulation alone. However, the magnitude of this effect was small compared to the total dynamic range of the system as well as the positive effect previously observed using iDC amplitude modulation [1]. It is the authors' opinion that a combined iDC + PFM approach is unlikely to provide enough functional benefit to justify further development towards chronic stimulation studies. Continued research into the use of

iDC for vestibular modulation should instead focus on iDC amplitude modulation. Regardless, these results continue to shed light onto how iDC interacts with the vestibular afferents and how it might effectively be harnessed for potential therapeutic benefit in this system.

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Fig. 1. Example stimulus waveforms. (A) A 100 μA biphasic pulse delivered without DC. (B) A 100 μA biphasic pulse delivered in conjunction with a 30 μA anodic iDC baseline. Dashed line indicates 0 μA current.

Fig. 2.

Electrically evoked VOR traces in implanted chinchillas. (A) Representative trace indicating the pulse frequency modulation waveform (pulse rate over time) delivered to the semicircular canal. (B-C) Left eye velocity traces in response to left posterior canal stimulation without iDC (B), and with a +30 μ A iDC baseline (C). Solid lines indicate movement in the plane of the horizontal (Z) left anterior/right posterior (LARP) and right anterior/left posterior (RALP) canals. Arrowheads indicate the peak excitatory (black) and inhibitory (grey) eye velocities for a single PFM waveform.

Fig. 3.

Maximum peak eye response magnitude for excitatory (A) and inhibitory (B) electrically evoked stimuli when no DC was applied and across all DC baselines. Solid line and error bars indicate the mean and the standard error of the mean. Circles indicated responses from posterior canals, and squares indicate responses from superior canals. Dashed lines indicate responses from the same canal. Asterisks indicate an outlier that was excluded from the statistical analysis.

Fig. 4.

Peak eye response velocity in response to pulse frequency modulation as a function of pulse amplitude and baseline intensity for excitatory (A) and inhibitory (B) eye rotations.

Asterisks indicate a statistically significant difference compared to the 0 μA iDC control, which is outlined with a dashed box (2-way ANOVA; $P < 0.05$; $n = 4$ canals, 3 animals).

Error bars indicate standard error of the mean (SEM).

Fig. 5.

Box-and-whiskers plot of angle of axis misalignment for excitatory and inhibitory eye rotations as a function of iDC baseline. Misalignment angle did not vary significantly between PFM and PFM+iDC conditions for either excitatory (2-way ANOVA; $P = 0.97$; $n = 4$ canals, 3 animals) or inhibitory (2-way ANOVA; $P = 0.72$; $n = 4$ canals, 3 animals) eye rotations.