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Research report

Tonic eye movements induced by bilateral and unilateral galvanic vestibular stimulation (GVS) in guinea pigs

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ABSTRACT

Galvanic vestibular stimulation (GVS) stimulates primary vestibular afferents innervating the semicircular canals (SCCs) and otoliths found in the inner ear of humans and other mammals, including guinea pigs. To determine which pathways contribute to eye movements generated by this artificial vestibular stimulation in guinea pigs, low current intensities of GVS were passed either bilaterally between the tensor-tympani muscles of the two ears (up to 30 μA) or unilaterally between one tensor-tympani electrode and an indifferent on the back of the neck (up to 60 μA). Both forms of GVS were found to selectively generate tonic eye movements without nystagmus, characteristic of the otolith-ocular reflex; the axis of eye rotation did not align with any semicircular canal plane, but was oriented close to the expected axis of eye rotation that would occur in response to the net stimulation of otolith afferents. The induced eye rotation was predominantly vertical with a smaller horizontal deviation and very little torsion. Consistent with the results of previous human studies, the tonic eye movements were found to exhibit bilateral gain enhancement, whereby bilateral GVS generated twice the amplitude of eye rotation as unilateral anodal or cathodal stimulation alone. Eye movement responses to unilateral GVS were symmetrical in amplitude during equivalent intensities of anodal and cathodal stimulation, consistent with the known responses of more regularly and intermediately discharging primary vestibular afferents to GVS. These results together suggest that more regularly discharging otolith-ocular projections may mediate the tonic changes in eye position induced during maintained, low-intensity GVS in guinea pigs.

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1. Introduction

Mammals regulate their gaze during self motion to acquire visual information about obstacles in the world. Although visual feedback from optic flow can help generate eye movements to stabilize the retinal image (Howard, 1982; Miles et al., 1986), the vestibuloocular reflex (VOR) provides superior temporal efficiency for maintaining stable gaze during head movement (Precht, 1979; Smith and Curthoys, 1989; Angelaki and Cullen, 2008). The primary vestibular afferents innervating the semicircular canals (SCCs) and otoliths carry information about head movements, but vary broadly in their discharge characteristics and sensitivity to natural and galvanic stimulation (Goldberg et al., 1984). Galvanic stimulation passed in and around the inner-ear modulates the resting activity of primary vestibular afferents, whereby anodal galvanic currents reduce the activity of primary vestibular afferents, whereas cathodal galvanic currents increase the activity of these afferents (Goldberg et al., 1984; Baird et al., 1988; Kim and Curthoys, 2004). The sensitivity of peripheral vestibular neurons to GVS is known to correlate with their discharge variability; neurons with greater sensitivity to GVS tend to also exhibit greater irregularity in resting discharge. The present study sought to determine the primary input to afferent pathways that contribute to eye movements induced during GVS.

Studies have shown that the effects of constant-current GVS on afferent activity at the vestibular periphery can generate eye movements in normal humans (e.g., Zink et al., 1997; Watson et al., 1998; MacDougall et al., 2003). The studies observed nystagmus indicative of primary SCC afferent stimulation and a tonic shift in the beating field of the eyes toward an ear stimulated by anodal current and away from an ear stimulated by cathodal current (e.g., Zink et al., 1997; MacDougall et al., 2003). The shift in the beating field (the local deviation in average eye position from central viewing) was interpreted as being caused by stimulation of primary otolith afferents. This is consistent with the view that human eye movement responses to GVS depend on stimulation of otolith afferents and not just primary SCC afferents (Wardman and Fitzpatrick, 2002). This pattern of eye movement mediated by SCC and otolith stimulation was observed at all current intensities of GVS delivered (0.8 mA to 5.0 mA), including near-threshold

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levels of stimulation (MacDougall et al., 2002). The similarity in eye-movement responses across intensities suggests that SCC-ocular and otolith-ocular pathways activated during GVS are gated by similar thresholds among second-order vestibular neurons in humans. This similarity in threshold complicates the task of determining the source of afferent pathways that contribute to eye movements induced during GVS.

One way to determine end-organ contributions to GVS-induced eye movements is to study eye movements in non-human mammals that do appear to have different centrally-gated thresholds for GVS. Kim (2009) identified a difference between the thresholds of tonic and phasic components of eye-movement responses to maintained constant-current GVS in guinea pigs. The phasic horizontal and vertical nystagmus induced during high-intensity GVS was consistent with the maintained stimulation of horizontal and vertical SCC afferents. The tonic shift in eye position without nystagmus induced during low-intensity GVS was consistent with the maintained stimulation of otolith afferents. This was further supported by the absence of adaptation and habituation in these tonic eye-movement responses, as habituation has not previously been implicated in the activity of central vestibular neurons receiving input from primary otolith afferents (Courjon et al., 1987). These observations suggest that eye movements induced during low-intensity GVS – below the threshold to induce nystagmus – are likely to depend primarily on the activation of otolith-ocular pathways.

The tonic properties of eye movements observed during low-intensity GVS may also be mediated by response dynamics associated with the discharge regularity of primary vestibular neurons. During maintained constant-current stimulation, irregularly discharging afferents tend to adapt more rapidly to maintained galvanic stimulation than regularly discharging afferents (Baird et al., 1988; Kim and Curthoys, 2004). The tonic properties of regularly discharging afferents may account for the tonic eye movement responses induced by GVS. Regularly discharging afferents also tend to have high-firing rates and lower sensitivity to galvanic stimulation, whereas irregularly discharging afferents tend to have lower firing rates and higher sensitivity to galvanic stimulation. For this reason, irregularly discharging afferents generate strong asymmetries in their responses to anodal and cathodal stimulation due to their low firing rates and high sensitivity for galvanic stimulation (Baird et al., 1988; Kim and Curthoys, 2004). The same studies showed that regularly discharging afferents respond symmetrically to anodal and cathodal stimulation.

Although both irregularly and regularly discharging afferents project within VOR pathways (Highstein et al., 1987; Boyle et al., 1992), some evidence suggests there may be greater emphasis on the activity of more regularly discharging afferent projections in mediating the VOR to brief angular head accelerations (Minor and Goldberg, 1991; Angelaki and Perachio, 1993; Chen-Huang et al., 1997). Minor and Goldberg (1991) showed that ablating anodal currents that were sufficient to silence the activity of irregularly discharging neurons did not affect normal VOR in monkeys. However, the discharge characteristics of primary vestibular afferents that mediate more tonic changes in eye position still remain unclear.

To assess whether irregularly discharging afferents mediate tonic gaze holding in guinea pigs, the present study applied low-intensity GVS in guinea pigs that was sufficient to activate tonic responses characteristic of the otolith-ocular reflex. Guinea pigs were used because they have an extensive physiological profile determined in previous studies using identical stimulation procedures (Kim and Curthoys, 2004; Kim, 2004, 2009). Whereas cathodal GVS increases afferent firing rate linearly in guinea pigs, anodal current is known to generate non-linear declines in the firing rate of more irregularly discharging afferents; the low firing rate of irregularly discharging afferents causes them to be silenced by small intensities of GVS. This asymmetric response does not occur among more regularly discharging afferents, which have higher resting discharge rates that prevents the cutoff in their discharge during anodal GVS (Kim and Curthoys, 2004). If irregularly discharging primary otolith afferents preferentially mediate GVS-induced eye movements, then unilateral anodal and cathodal stimulation should induce asymmetrical tonic eye deviations. Alternatively, if more regularly discharging afferents contribute to GVS-induced eye movements, then the symmetry of regularly discharging afferent responses to anodal and cathodal GVS should generate symmetrical eye-movement responses.

2. Materials and methods

2.1. Subjects

Twelve female, normal and healthy pigmented guinea pigs were used according to experimental and surgical protocols approved by the Animal Ethics Committee (AEC) at the University of Sydney. All animals were naive to experimentation and weighed between 550 and 900 g.

2.2. Initial surgery

Subjects were anaesthetised using intramuscular injections of Ketamil (ketamine hydrochloride, 100 mg/kg, Troy Laboratories) and Xylase (xylazine, 4 mg/kg, Parnell Laboratories). Following anaesthesia, the dorsal surface of the skull was exposed, and four stainless-steel screws (0–80 UNF × 1/8″) were implanted around Bregma. These screws provided an anchor for a plastic rod of square cross-section (3.3 mm × 3.3 mm × 30 mm) that was embedded in a thick layer of dental acrylic. The rod was orientated along the inter-aural axis of each subject as it was restrained in a nose bar 40° pitch downward. When set, the head holder restrained the head nose-down to align the plane of the horizontal SCCs closely to the earth-horizontal plane (see Curthoys et al., 1975). This head holder also served to minimize head movement in pitch, roll and yaw during scleral search coil recording.

Middle-ear stimulating electrodes were constructed from short lengths of stainless-steel syringe needles (25G × 2 mm, Nipro™). A small hole was made in the temporal bone to expose the attic of the middle ear, and a stimulating electrode was implanted into the tensor-tympani muscle. This was done bilaterally in all twelve animals, and the drilled openings were then sealed with dental acrylic. The insulated electrode leads were soldered to two pins of a standard 8-pin IC socket, which was attached to the head holder using dental acrylic. Two other pins were soldered to each other and to at least one of the head-holder anchor screws, providing the reference for unilateral GVS. For post-operative pain management, animals were given intramuscular injections of Temgesic™ (0.03 mg/kg Buprenorphine, Reckitt & Colman). Recording commenced at least one week after surgery in order to ensure there was no residual effect of ketamine on GVS-induced eye movements.

2.3. Eye movement recording

The position of each eye was tracked using a 3D search-coil method (see Robinson, 1963; Gilchrist et al., 1998). The detector coil of each eye was approximately 2 mm in diameter and consisted of 10 turns of wire (20 μm) having a combined weight of less than 10 mg. The two coils were oriented orthogonal to one another and bonded with epoxy (Hess and Dieringer, 1991). This constituted a single 3D coil used to detect changes in the position of one eye. Using two eye detector coils and having three transmission channels, 12 anti-aliased output voltages were sampled at a rate of 500 Hz using a 16-bit interface analogue-to-digital converter operating on a PC running LabVIEW 4 under Windows 95.

An animal was first restrained in a canvas bag with Velcro straps and then placed in a specially designed Perspex holding box. The rigid holding compartment had an attachment that mated to the head holder, securing the mid-point between the two eyes within the centre of a cube transmitter field (20 cm × 20 cm × 20 cm). The corneas of each eye were anaesthetised with sterile ophthalmic drops (containing 0.5% Amethocaine Hydrochloride, Chauvin Pharmaceuticals). Eye coils were placed on the sclera of each eye using less than one drop of cyanoacrylate adhesive (Pronto™ CA8, 3 M). Following each eye-movement recording session, the two eye coils were carefully removed with forceps. This removal leaves very little residue and causes no apparent discomfort to the animal. Animals were given apple reward and allowed half an hour of rest between the end of a test session and return to the animal house in order for corneal sensitivity to recover.

2.4. Calibration of the recording system

Prior to testing, the two 3D eye coils were calibrated in vitro. Each eye-coil was mounted on a carefully designed “dummy animal”, consisting of a guinea-pig

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