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Research paper

The adequate stimulus for mammalian linear vestibular evoked potentials (VsEPs)

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ABSTRACT

Short latency linear vestibular sensory evoked potentials (VsEPs) provide a means to objectively and directly assess the function of gravity receptors in mammals and birds. The importance of this functional measure is illustrated by its use in studies of the genetic basis of vestibular function and disease. Head motion is the stimulus for the VsEP. In the bird, it has been established that neurons mediating the linear VsEP respond collectively to the rate of change in linear acceleration during head movement (i.e. jerk) rather than peak acceleration. The kinematic element of motion responsible for triggering mammalian VsEPs has not been characterized in detail. Here we tested the hypothesis that jerk is the kinematic component of head motion responsible for VsEP characteristics. VsEP amplitudes and latencies changed systematically when peak acceleration level was held constant and jerk level was varied from ~0.9 −4.6 g/ms. In contrast, responses remained relatively constant when kinematic jerk was held constant and peak acceleration was varied from ~0.9 to 5.5 g in mice and ~0.44 to 2.75 g in rats. Thus the mammalian VsEP depends on jerk levels and not peak acceleration. We conclude that kinematic jerk is the adequate stimulus for the mammalian VsEP. This sheds light on the behavior of neurons generating the response. The results also provide the basis for standardizing the reporting of stimulus levels, which is key to ensuring that response characteristics reported in the literature by many laboratories can be effectively compared and interpreted.

1. Introduction

The short latency linear vestibular evoked potential (VsEP) has become a valuable tool in evaluating vestibular function in mammals and birds (e.g., Jones and Jones, 1999; Jones et al., 2005; Alagramam et al., 2005; Jones et al., 2006; Jones et al., 1998a). This is particularly true for studies in the mouse, an animal model that brings a notable advantage to the study of the molecular and genetic basis of vestibular function and disease.

The linear VsEP is an electrical response initiated within the labyrinth (Jones and Jones, 1999; Jones and Pedersen, 1989; Jones, 1992; Jones et al., 1997; Weisleder et al., 1990; Plotnik et al., 1997; Bohmer et al., 1995) by gravity receptors (Jones and Jones, 1999; Jones et al., 2004, 1999) and generated by macular primary afferents and central relays (Nazareth, 1991; Nazareth and Jones, 1991, 1998). The VsEP is produced in response to transient linear acceleration of the head. What we glean from the results of VsEP testing depends in part on our understanding of how the response is elicited. For example, revealing the effective component of stimulus motion (i.e. the adequate stimulus) for the VsEP response provides insight regarding what kind of primary afferent discharge behavior is required and this in turn may suggest candidate neural types that mediate the response.

In the bird, the adequate stimulus for the VsEP has been shown to be the rate of change in acceleration (also known as kinematic jerk) rather than peak acceleration (Jones et al., 1998b). This was a key observation that permitted for the first time the precise prediction of normal response patterns under varying stimulus conditions. Although there have been some preliminary data

Abbreviations: C57, C57BL/6J mouse strain; dB SPL, decibel sound pressure level re: 20 micropascals RMS; iso-accel, iso-acceleration; Nox3, Nox3^{het} (+/−) heterozygote mouse strain; R^2, coefficient of determination; rmANOVA, repeated measures analysis of variance; RMS, root mean square; VsEP, vestibular sensory evoked potential.

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reported for the rat (Lange, 1988; Lange and Jones, 1989, 1990; Bothwell and Jones, 1997), no detailed evaluation in the mouse has been reported regarding the answer to this important physiological question.

In the present study we tested the hypothesis that the adequate stimulus for the mammalian VsEP is linear kinematic jerk. To test this hypothesis we set out to show that linear VsEP responses are independent of peak acceleration when stimulus jerk levels are held constant and strictly dependent on jerk when stimulus peak acceleration is held constant. Because of their wide use and potential for scientific inquiry, we chose to complete these studies in the rat and mouse. We include two strains of mice: the widely used normal adult C57BL/6J and the Nox3^{het} (+/−) heterozygote. We include Nox3^{het} (+/−) because it is often used as a control for studies of otoconia-deficient mice (e.g., Nox3^{het} (−/−)).

2. Methods

2.1. Animals

Five Sprague Dawley rats (males, 36–41 days old) weighing between 120g and 160g were used. Ten normal adult C57BL/6J (abbreviated: C57; 6–7 months old, 3 males and 7 females weighing 25–45gm) and ten Nox3^{het} (+/−) heterozygote mice were used (background C57BL/6JEi, 3 & 4 months old, 5 male and 5 female weighing 20 and 30g). The phenotype of the heterozygote Nox3^{het} (+/−) is normal in that these animals have normal otoconia, demonstrate robust VsEPs and are good swimmers (Jones et al., 1999, 2008).

2.2. Anesthesia

Rats were anesthetized using an intraperitoneal (ip) dose (0.10 ml/100g,) of a Ketamine (18 mg/ml)/Xylazine (2 mg/ml) mixture. Mice were anesthetized with 7 μl/g of the Ketamine/Xylazine. Anesthesia was maintained in both species using additional doses (0.05 ml) as needed.

2.3. Stimulus generation

The methods used for stimulation in the present study have been described in detail previously (e.g., Jones and Jones, 1999; Jones et al., 2002; Jones and Jones, 2007; Jones, 2008). Jerk stimuli were produced by applying voltage ramps (digital to analog conversion time 20 μs/point) to a commercial power amplifier. The power amplifier in turn drove the motion of an electromechanical shaker (Labworks, Inc. Model ET2-203). As described below, the duration of the voltage ramp was adjusted to produce different peak acceleration levels while keeping jerk levels constant. Stimuli were presented at a rate of 17/s. A calibrated accelerometer (100 mv/g, $g = 9.81$ m s^{-2}) was mounted on a solid right-angle aluminum plate that was bolted to the tip of the shaker piston. The accelerometer output was electronically differentiated to provide a calibrated jerk monitor voltage. Both kinematic acceleration and jerk were monitored throughout the studies. The animal's head was affixed to this shaker platform using a head clip (mice) or screw (rats) as described below.

2.4. Stimulus coupling to the skull

In rats, the mechanical coupling to the skull was surgically prepared and was similar to that described elsewhere (Jones and Jones, 1999; Jones et al., 1999, 2002). Two self-tapping stainless steel screws were placed on either side of the coronal and sagittal sutures and used to anchor the skull to the shaker coupling assembly. A stainless steel machine screw was inverted and embedded in fast setting plaster along with the two skull screws. The inverted screw was then bolted to the shaker platform.

A non-invasive head coupler was used for studies in mice (Jones and Jones, 2007; Jones, 2008). The animal's head was held snuggly in a spring-loaded clip, which in turn was coupled to the shaker platform. All animals were placed supine on a stationary heated base and the head was suspended beyond the edge of the base and attached to the shaker platform with nose oriented upward. Shaker motion was executed along the animal's naso-occipital axis (Jones and Jones, 1999; Jones, 2008).

2.5. Iso-jerk and iso-acceleration stimuli

As noted above, we used acceleration ramps as stimuli. Given that kinematic jerk is the first time derivative of acceleration (in g), it follows that the slope of the acceleration ramp (slope = da/dt = jerk in g/ms) represents the corresponding jerk magnitude in g/ms. If one keeps the slope constant, then the peak acceleration is a function only of the duration of the acceleration ramp. We refer to the duration of the ramp as the stimulus rise time. Therefore, one can hold jerk level constant (iso-jerk conditions, Fig. 1) and systematically change the peak acceleration by increasing or decreasing the rise time. If responses are triggered by peak acceleration, then responses will change systematically with different rise times. Here we recorded VsEP responses under iso-jerk conditions using rise times of 0.5, 1, 2 and 4 ms (Fig. 1). On the other hand, if one holds peak acceleration constant (iso-acceleration conditions, Fig. 2) and systematically varies the rise time, then jerk levels must systematically change with different rise times in order to maintain a constant peak acceleration. Under these conditions, if responses are triggered by peak acceleration, then response amplitudes will be unaffected by differing rise times. If however they are triggered by jerk components of the motion, then response amplitudes will change systematically with rise time. Here we recorded VsEP responses under iso-acceleration conditions using rise times of 0.5, 1, 2 and 4 ms (Fig. 2). Stimulus levels were reported in absolute units

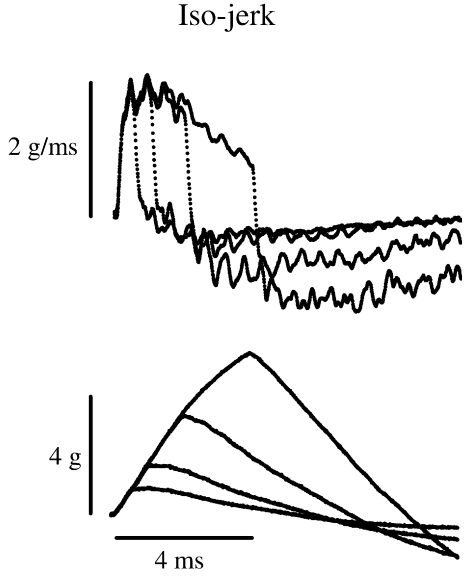

Fig. 1. Iso-jerk stimulus protocol. Recordings of stimulus jerk (Top, in g/ms) and acceleration (Bottom, in g). Top: The duration (rise time) of the jerk stimulus (g/ms) is varied (0.5, 1, 2 & 4 ms) while the peak amplitude is held constant. Bottom: Peak acceleration (g) increases systematically (~0.9, 1.7, 3.3 and 5.5 g) with increasing jerk duration. Calibration bars indicate scales for acceleration, jerk and time.