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Effect of common antivertiginous agents on the high velocity vestibulo-ocular reflex

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HIGHLIGHTS

- Does the mode of action of antivertiginous agents cause impairment of the human vestibulo-ocular reflex (VOR)?
- Video head impulses showed that VOR gain remained unaffected independent of substance class.
- The high frequency VOR remains robust to pharmacological perturbations.

ABSTRACT

Objective: It has long been suggested that antivertiginous medications exert their symptomatic effect through inhibition of the vestibulo-ocular reflex (VOR). We tested this hypothesis by directly measuring the VOR after administration of three agents from different substance classes: an antihistamine, a benzodiazepine and a calcium channel antagonist.
Methods: The gain and the variability of the high velocity VOR was assessed using video head impulses (vHIT) under the following conditions: baseline, after dimenhydrinate, after diazepam and after cinnarizine.
Results: We found that all three medications did not change any VOR gain or variability parameter: At 60 ms, the gain was 0.95 at baseline, 0.99 under dimenhydrinate, 0.99 under diazepam and 0.96 under cinnarizine. The gain variability across repetitive head impulses remained also uninfluenced.
Conclusions: The human high frequency VOR remains robust to pharmacological perturbations at common clinical doses and the assumption that symptomatic vertigo relief is achieved merely through impairment of the VOR requires re-examination.
Significance: Alternative mechanisms of pharmacological action might be operant, such as the modulation of vestibulo-cortical pathways, a differential effect on the low frequency VOR and an altered sensitivity to drugs in acute unilateral vestibulopathy.

1. Introduction

The vestibulo-ocular reflex (VOR) is at the core of examining, diagnosing and understanding vestibular syndromes. Its functional significance lies in the maintenance of clear vision when the head moves. Mediated by three-neuron reflex arcs (Lorente de Nó, 1933; Szentagothai, 1950), the rotational VOR produces a slow-phase eye movement that compensates for horizontal, vertical or torsional head rotations. Although many physiological details had already come to light before the 1980s (Baker et al., 1981), it was not until 1988 that a simple clinical method, the head impulse test (HIT), became available that could be used to assess the integrity of the VOR at the bedside (Halmagyi and Curthoys, 1988). Nowadays, the HIT can be quantified by both clinicians and basic scientists using high-frame-rate, head-mounted video-oculography devices (Halmagyi et al., 2001; Bartl et al., 2001), and has been already successfully used in the study of the influence of exogenous substances such as ethanol on vestibular function (Roth et al., 2014).

With the head still, both right and left vestibular afferents exhibit a resting discharge rate of about 90 spikes/s (Goldberg and Fernandez, 1971). Thus, unilateral vestibular nerve damage leads to a relative decrease of the ipsilateral spike rate as compared

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to that of the opposite vestibular nerve. This has two consequences: First, a faulty VOR slow-phase is initiated which drives the eyes towards the pathological side. Before reaching the physical limit of the orbit, this slow phase is interrupted by a corrective saccade that returns the eyes to the approximate center of the oculomotor range. This biphasic movement occurs repeatedly, resulting in the classical pattern of the peripheral vestibular jerk nystagmus. Second, ascending vestibulo-thalamic pathways convey this asymmetric activity to the cortex (Zwergal et al., 2009), producing a self-rotation sensation or vertigo.

In the past two decades, great progress has been made in the treatment of a variety of vestibular syndromes (Strupp et al., 2013). However, symptomatic treatment for acute vertigo spells is still dominated by the classical vestibular suppressants. Although highly efficient in many cases, their exact mode of action is not clear. It is generally assumed that these agents, which show affinity to different receptors, ultimately act as suppressants of both nystagmus and spinning sensation, presumably by reducing the pathologically initiated VOR. Here, we aimed to verify this assumption by testing the VOR performance of normal subjects after administration of three vestibular suppressants from different substance classes: an antihistamine (dimenhydrinate), a benzodiazepine (diazepam) and a calcium channel antagonist (cinnarizine).

2. Subjects and methods

2.1. Participants

Compensatory eye movements were measured during horizontal head impulses in 12 healthy adults (5 women/7 men, mean age: 29.7 years, range: 21–43 years). No participant had a history of a neurological or vestibular disorder or was using any form of medication at the time of the study. All subjects gave written informed consent for participation in the study which was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Department of Neurology of the University of Athens.

2.2. Recording method

Eye movements were measured by use of a goggle mounted with a lightweight, high-frame-rate camera (EyeSeeCam®, Interacoustics, Denmark). Head movements were recorded simultaneously by means of a gyroscopic inertial measurement unit. Data were digitized at 220 Hz. Subjects were seated 1.5 m from a projection wall with the video goggle tightened around their head and the camera adjusted so that the iris patterns were clearly visible and the pupil was centered. For calibration, subjects made saccades to five laser dots projected on the wall (straight ahead and 8.5° right, left, up and down). The examiner stood behind the participant holding the subject's head at the jaw and delivered unpredictable head impulses in a horizontal plane. Head impulses were 10°–20° in amplitude with a peak velocity of more than 150°/s. At least ten impulses were performed to each side.

2.3. Data processing

Instantaneous gain values were calculated by the EyeSeeCam software at 60 ms after head movement onset, by calculating the ratio of instantaneous eye to head velocity. The median value of all head impulses was taken for further analysis. As an alternative measure, the velocity regression VOR gain was also computed, which represents the slope of the linear regression plot obtained from all eye-head velocity data pairs. The standard deviation of the median gain at 60 ms and the 95% confidence interval around the slope of the regression line were taken as measures of variability. Head impulses were automatically detected from the data according the following criteria: Peak angular head velocity had to be reached within the first 150 ms after onset of head impulse and had to exceed 70°/s, while head acceleration had to exceed 1000 °/s^2. If the relevant component of head velocity changed sign during the impulse or if the direction of the rotation axis of the head at maximal velocity was not within ±45° of the intended direction, the head impulse was discarded. The onset of the head impulse was defined as the time when head velocity exceeded 20°/s.

2.4. Conditions

Subjects were tested in four different conditions. The first was the baseline recording session in which the participants took no medication. Then, the four post-drug recording sessions followed in a pseudorandomized order in one-week intervals. During these sessions subjects received a single dose of either 50 mg dimenhydrinate, or 5 mg diazepam or 25 mg cinnarizine per os. The experiment started 90 minutes after drug intake. Three subjects were tested additionally at 180 minutes after drug intake in order to minimize the possibility of a suboptimal time-window bias of the 90-minutes-recordings.

2.5. Statistics

Statistical differences in both instantaneous and velocity regression VOR gain for the four different conditions (baseline, dimenhydrinate, diazepam and cinnarizine) were tested with repeated measures analysis of variance (ANOVA). Significance was set to P equal to 0.05.

3. Results

At baseline, all subjects had VOR-gain values above 0.75 for both rightward and leftward head impulses, which is the lower normal limit in our laboratory. Fig. 1 depicts head impulses of one subject before and after administration of the three medications under study. The mean baseline vHIT gain value over all 12 subjects at 60 ms was 0.95 and the mean regression slope gain was 1.03 for rightward head rotations. Similarly, for leftward head impulses gain values were 0.98 and 1.03 respectively. After diazepam, dimenhydrinate and cinnarizine administration gain values remained remarkably stable. This was true for the 60 ms and the regression slope gain calculations and was observed in both rightward and leftward head impulses. Accordingly, statistical testing using repeated measures ANOVA revealed no significant differences. The 60-ms VOR gain values are presented graphically in Fig. 2, while Table 1 summarizes the descriptive statistics and the ANOVA results.vHIT gain variability (60 ms gain) amounted 0.08 for rightward and 0.07 for leftward head impulses in the baseline condition. Here again, no difference has been observed after diazepam, dimenhydrinate or cinnarizine administration. This held also for the variability of the regression slope gains. Table 2 summarizes the different variability measures and the statistical comparisons.

Similarly, the recordings performed at 180 min after drug intake in three subjects showed no drug effects in any of the measured parameters (these results are presented as supplementary information – supplementary Tables 1 and 2; supplementary Fig. 1).