THE VESTIBULO-OCULAR REFLEX AND VELOCITY STORAGE IN SPINOCEREBELLAR ATAXIA 8

J.H. ANDERSON[1*], M.C. YAVUZ[2], B.M. KAZAR[3], P. CHRISTOVA[1], AND C.M. GOMEZ[4]

[1] Department of Otolaryngology, University of Minnesota, Minneapolis, MN, USA; [2] Department of Computer Science and Engineering, University of Minnesota, Minneapolis, MN, USA; [3] Department of Electrical and Computer Engineering, University of Minnesota, Minneapolis, MN, USA and [4] Department of Neurology, University of Minnesota, Minneapolis, MN, USA

INTRODUCTION

The vestibulo-ocular reflex (VOR) helps to maintain gaze, the position of the eyes in space, during head movement. During brief, transient rotations the angular VOR causes the eyes to rotate opposite to the head rotation, thereby helping to keep the visual world stable on the retina. However, when the movement of the head is sustained, the VOR will no longer be present. After reaching a constant head velocity, the eye velocity will decay to zero in darkness. The characteristics of this decay are determined in part by a neural network, referred to as velocity storage (15, 17), which helps to prolong the time course for decay so that the VOR continues even after the neural activity of the vestibular afferents has returned to baseline. In addition, there can be a reversal in the direction of the eye velocity (i.e., the eyes move in the same direction as the head) that is dependent on both adaptation in the transduction process and the brainstem network (7, 8).

The aim of the present work was to develop a model for the decay and reversal of the horizontal VOR in patients who have spinocerebellar ataxia (SCA) subtype 8 (13). Clinical evaluations and MRI (5) indicate that the pathology in SCA8 includes a degeneration of the cerebellum, a structure that is important for controlling the gain and direction of the VOR (19) and the spatial relationship of the VOR to a gravitoinertial reference frame (11, 16). The SCAs are a group of neurodegenerative diseases characterized by progressive instability of posture and gait, incoordination, ocular motor dysfunction, and dysarthria due to degeneration of cerebellar and brainstem neurons. Recent studies have established that there are more than 20 genetically distinct subtypes, and clinical observations suggest that eye movements and postural stability are universally but differentially impaired across the subtypes. In SCA8 the pathology seems primarily to involve the cerebellum and not other CNS structures.

Previous studies with the SCAs and episodic ataxia II have shown that otolith-ocular reflexes (1, 4, 6) and visual-vestibular interactions (18) are impaired, and there can be either an increase (9) or decrease (3) in the gain of the angular VOR,

Address for correspondence: Dr. J.H. Anderson, Department of Otolaryngology, University of Minnesota, Mayo Mail Code 396, 420 Delaware St. S.E., Minneapolis, MN 55455,USA

depending on the SCA subtype. However, the effects of cerebellar dysfunction in the SCA on the velocity storage mechanism have not been investigated. In the present study we propose a model to characterize the contributions of the velocity storage mechanism to the horizontal angular VOR in SCA8. This is based on the model of Raphan et al (15) wherein the pathways carry physiological signals, and there are direct and indirect (which contribute to the velocity storage) pathways that represent projections to the motor neurons innervating the eye muscles. In addition there is another pathway carrying an eye position signal that feeds into the velocity storage network. This feedback of an eye position signal contributes to the reversal in the direction of the VOR.

METHODS

Data were collected from 12 normal control subjects and 3 patients. The SCA8 patients were defined genetically (13), and based on the previously reported description of clinical findings in SCA8 (5), the patients were characterized as having moderate to severe disease. EOG electrodes were used to record the position of the eyes in the head while the subjects sat on a chair (attached to a Contraves-Goerz 826 rate table) that was rotated in the horizontal plane. The head was held in a restraint attached to the chair (so that there was no neck movement), and the subject was in complete darkness. The reflex eye movement (VOR) was initiated by a short period of constant angular acceleration, 10 deg/sec^2 (for 18 seconds) or 20 deg/sec^2 (for 9 seconds), causing a ramp change in angular velocity of the head. A LabVIEW (National Instruments) data acquisition program was used to sample the EOG recording of the VOR and the tachometer signal (angular velocity of the rate table) at 200 Hz.

Matlab (The Mathworks) programs were used to digitally filter the sampled data, differentiate the eye position signal, and remove the quick phases from the eye velocity. The resulting slow phase eye velocity, referred to as the compensatory part of the VOR, was used for the modeling studies. Simulink (The Mathworks) was used to set up the model shown in Figure 1. It includes the eye velocity storage mechanism proposed by Raphan et al (15) and an additional pathway identified as "Eye Position Feedback". The eye velocity signal is integrated by the term, $1/(s + a_3)$, and feeds into the velocity storage network as negative feedback. Four parameters in the model (g_1, g_2, g_3, h) were adjusted in order to best fit of the model to the eye velocity data for individual trials. The parameter g_1 is the gain for a direct vestibular pathway relaying a velocity signal from the inner ear to the extra-ocular motoneurons; g_2 is the gain for the pathway to the integrator, 1/s, of the velocity storage mechanism; h is the gain for negative feedback to that integrator; g_3 is the gain for the eye position feedback. The fitting was done using fmincon, a Matlab routine for minimizing the RMS error (between the model and the data) with constraints. The constraints were the following: $g_1 > 0$, $g_2 > 0$, $g_3 < 0$, $h < 0$, and a_3 was set equal to 0. The cupula dynamics and hair cell transduction process were lumped together and represented by the following:

$$\frac{1}{(t_c s + 1)} \frac{t_a s}{(t_a s + 1)}$$

where s is the Laplace operator, $t_c = 5.7$ sec, and $t_a = 80$ sec. The t_a term represents adaptation in the vestibular afferent firing frequency (7).
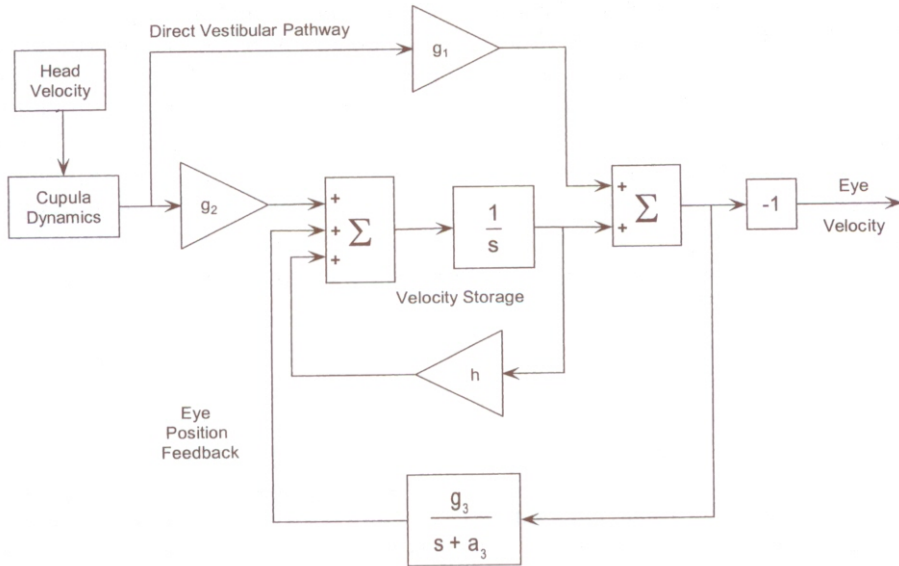
Fig. 1. - *Model of velocity storage for the horizontal vestibulo-ocular reflex.*
The model is adapted from Raphan et al. (15). Head velocity is the input and eye velocity is the output of the model. The minus sign indicates that the slow phase component of a vestibular nystagmus is normally opposite to the head acceleration during the initial part of a transient head acceleration. The four terms, g_1, g_2, g_3, and h are gain terms for the respective pathways, and is the Laplace operator. The term "cupula dynamics" represents the inner ear transduction process, including the dynamics of the cupula, vestibular hair cells, and encoding in the afferent nerves.

RESULTS

An example of the VOR response for one trial in one SCA8 patient is shown in Figure 2A. The angular acceleration of the head was 20 deg/sec², causing a counter-clockwise rotation of the patient. The circles are the maximum eye velocity for individual slow phases of the VOR and the solid line is the best fit of the model (see Figure 1 and Methods) to the data. Note that initially the eye velocity was to the right, opposite to the direction of head rotation, but 20 to 30 sec. after the acceleration had ceased and the head velocity was constant, the direction of the eye velocity reversed and was to the left. In fact, this example shows the most pronounced reversal among the 17 trials included in this report. The value for the gain of the eye position feedback, g_3 (which contributes to this reversal), was $-7.4 *10^{-4}$, and the value for the ratio, g_2/g_1 which is ratio of the gains for the indirect pathway (to the velocity storage integrator) and direct VOR pathway (bypassing the integrator), was $19.9 *10^{-2}$ (Table 1). The magnitude of both these values was the largest across the SCA8 trials.

Figure 2B shows the mean ± SD region for the eye velocity of the model for the normals (dark shaded region) and SCA8 patients (lightly shaded region). The regions were calculated as follows. The parameter values that were obtained from the fit to each single trial were used to simulate a VOR during a head acceleration

Tab. 1. - *Values for the parameters of the velocity storage model that were optimized.*

	$h * 10^{-2}$		g_1		$g_2/g_1 * 10^{-2}$		$g_3 * 10^{-4}$		Trials	Subjects
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
SCA 8	-4.3	1.4	3.8	1.2	13.8	6.2	- 1.4	2.0	17	3
μSCA 8	-4.4		3.6		12.3		- 1.0			
Fig. 2A	- 3.8		3.1		19.9		- 7.4		1	1
Normal	- 3.0	2.4	3.9	1.0	8.1	4.7	- 0.1	0.2	54	12
μnorm	- 2.1		4.3		5.8		0.0			

of 10 deg/sec² in the counterclockwise direction (rotation to the left). These simulations were done for the fits to all trials in all subjects and included the trials with accelerations in both directions and with both magnitudes. These simulations were then averaged together to obtain the shaded regions. Note that the reversal for the patients is greater in magnitude and occurs earlier in time compared to normals.

Table 1 shows the mean and standard deviation of the values for the four parameters that were optimized. A multiple ANOVA and univariate F-tests showed that g_1, the gain of the direct pathway, was not significantly different between normals and the SCA8 patients. However, there were significant differences ($p < 0.01$) for the other three parameters that contribute to the velocity storage network. The magnitude of the mean value (averaged across the values for all the trials with all the
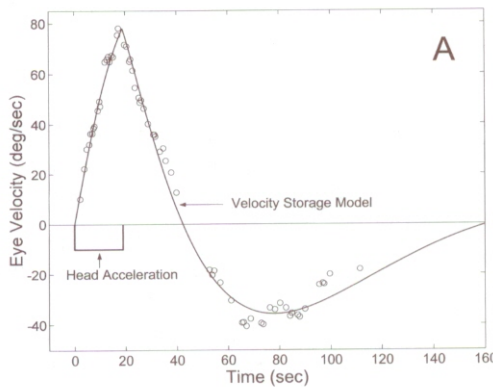

Fig. 2A. *Fit of model to eye velocity for one trial in an SCA8 patient.*
The open circles are the maximum eye velocity of individual slow phases of the VOR caused by acceleration (10 deg/sec²) of the subject in the horizontal plane (to the left) for 18 seconds. The solid line is the fit of the velocity storage model. The four terms that were adjusted had the following values: $h = -3.8*10^{-2}$, $g_1 = 3.1$, $g_2/g_1 = 19.9*10^{-2}$, $g_3 = -7.4*10^{-4}$. The data are from trial 3868_a026.
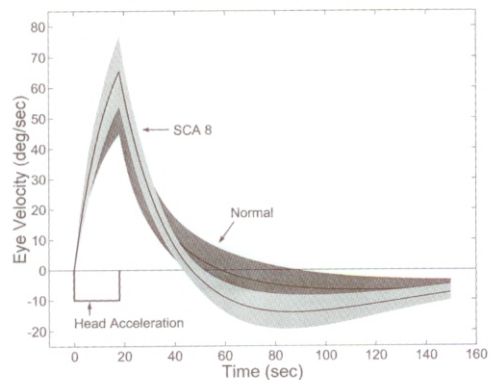
Fig. 2B. *Eye velocity of the model based on fits to the data from normal subjects (darkly shaded) and SCA8 patients (lightly shaded).* The solid lines are the mean curves and the shaded regions include ± 1 SD for 54 trials with normal subjects and 17 trials with SCA8 patients. The eye velocity is the VOR response to head acceleration (10deg/sec²) of the subject in the horizontal plane (to the left) for 18 seconds.

patients; designated as SCA8 and Normal in Table I) for g_3, the gain of the eye position feedback, was greater for the SCA8 patients ($1.4 *10^{-4}$) compared to the normals ($0.1 *10^{-4}$). Also, the magnitude of the values for g_2, the gain of the input to the integrator, and h, the feedback to the integrator, both were greater for the patients. Note that the larger value for h means that the time constant (1/h) for the integrator pathway had a lower value (33 sec. for Normal and 23 sec. for SCA8). Finally, Table I shows the parameter values for a fit of the model to the mean of the simulations for the fits to all the individual trials (designated as μ_{SCA8} and μ_{norm}). Although the numerical values are slightly different, the values for the patients still are greater than normal and the differences are significant ($p < 0.01$).

DISCUSSION

The present results show that there is a significant reversal in the direction of the horizontal VOR that is more pronounced in SCA8 compared to normals. Furthermore, simulations of a model suggest that this could be due to an increase in the gain of pathways in the eye velocity storage network and feedback of an eye position signal into the storage network in the brainstem. It should be noted that the present model does include a peripheral (inner ear and/or vestibular afferent) adaptation term that contributes to a small reversal in normal subjects. However, the changes in the velocity storage network cause the reversal to be greater in magnitude and to occur earlier in time.

Previous models of the VOR and the velocity storage mechanism have included a central adaptation operator that gives rise to a reversal in the direction of the VOR after a brief period of acceleration (7, 8, 14). Those models were based on a positive feedback pathway for the velocity storage (17) and feedback of an eye position signal that would combine with the vestibular afferent inputs to the brainstem. Consequently, all the vestibular pathways would be affected by the adaptation operator. In contrast, for the present model it is proposed that the eye position feedback acts only on the velocity storage network (as formulated by Raphan et al. (15)) and not on the "direct" vestibular pathway to the oculomotor neurons. This implies that only a subset of vestibular nuclei neurons would be affected by the eye position feedback. Furthermore, if those neurons were strongly influenced by the cerebellum, then that could account for the greater reversal in SCA8.

It has been suggested that reversals in the direction of a vestibular nystagmus (12), rebound nystagmus (12), and periodic alternating nystagmus (14) are all caused by the same central adaptation mechanism that is influenced by cerebellar dysfunction. The VOR data for SCA8 provide additional evidence for this. Clinically, SCA8 is characterized as a cerebellar ataxia with a neurodegeneration that causes marked cerebellar atrophy (5). Imaging and neuropathological studies could help to identify other regions of the brain that might be involved. Future physiological studies with SCA8 and other SCA subtypes, including those that have predominantly cerebellar pathology such as SCA5 and 6 and episodic ataxia

II, should provide new information about the selective vulnerability of neurons controlling vestibular reflexes.

SUMMARY

The autosomal dominant spinocerebellar ataxias (SCAs) are a group of neurodegenerative diseases characterized by progressive instability of posture and gait, incoordination, ocular motor dysfunction, and dysarthria due to degeneration of cerebellar and brainstem neurons. Among the more than 20 genetically distinct subtypes, SCA8 is one of several wherein clinical observations indicate that cerebellar dysfunction is primary, and there is little evidence for other CNS involvement. The aim of the present work was to study the decay of the horizontal vestibulo-ocular reflex (VOR) after a short period of constant acceleration to understand the pathophysiology of the VOR due to cerebellar Purkinje cell degeneration in SCA8. The VOR was recorded in patients with genetically defined SCA8 during rotation in the dark. Moderate to severely affected patients had a qualitatively intact VOR, but there were quantitative differences in the gain and dynamics compared to normal controls. During angular velocity ramp rotations, there was a reversal in the direction of the VOR that was more pronounced in SCA8 compared to controls. Modeling studies indicate that there are significant changes in the velocity storage network, including abnormal feedback of an eye position signal into the network that contributes to this reversal. These and other results will help to identify features that are diagnostic for SCA subtypes and provide new information about selective vulnerability of neurons controlling vestibular reflexes.

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