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Membrane properties of medium-lead burst neurons may contribute to dynamical properties of saccades

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Abstract- **Previous models of saccades use circuits with simple elements. Medium-lead burst neurons (MLBNs) fire only during saccades, and generate the eye velocity command. Omnipause neurons (OPNs) fire during fixation and pause during saccades in all directions. OPNs are assumed to inhibit MLBNs. MLBNs have been modeled with a single membrane time constant and a firing rate saturation. Therefore, circuit properties, and not properties of the neurons themselves, determine the dynamical properties of saccades. However, a recent study suggests that MLBNs may have another membrane property, post-inhibitory rebound depolarization, which plays a critical role in the generation of oscillations. This finding raises the question of the effect of OPN offset and rebound depolarization of MLBNs on saccades, because chemical lesions of the OPN region alter the dynamics of saccades. A new model with MLBNs that have two biophysical properties, post-inhibitory rebound depolarization and a threshold, produces behavioral changes in saccades after simulated OPN lesion that are consistent with experiment. We suggest that biophysical properties of MLBNs may contribute to dynamical properties of saccades, such as speed and latency.**

Keywords - **saccades, medium lead burst neurons, membrane property, omnipause neurons**

I. Introduction

Since Robinson [1], many models for the control of saccades (rapid eye movements used for re-fixation) have been proposed. In classical models [1-3], the saccadic system was commonly described as a negative feedback control circuit. Medium lead burst neurons (MLBNs) were described as premotor neurons, providing eye velocity command for saccades. The command was fed back and then integrated with a resettable integrator (Jürgens's scheme [3]), generating current eye displacement. The current displacement was compared with the desired eye displacement, generating motor error. Based on the motor error, MLBNs generate the velocity command. Omnipause neurons (OPNs), a class of saccade-related neurons with maintained activity that ceases during saccades, have been described as neurons that inhibit MLBNs (i.e., an inhibitory gate). Recent studies have focused more on neural processing (neural networks) for the motor control of saccades, based on discoveries of details of saccade-related neural activity in the brain stem (pons and superior colliculus, SC) and in the cerebellum [4-7]. The functional roles of the cerebellum and/or the SC in saccades has been intensively studied [5-7].

In all of the previous models, neurons, such as MLBNs, have been assumed to have very simple biophysical properties, at most a single membrane time constant and a firing rate saturation. Thus, the only saccadic property that can be assigned to the MLBNs is the saturation of peak velocity observed for saccades of large amplitude. No other function related to the dynamics of the saccade, such as speed or latency, has been assigned to these neurons.

A recent study has pointed out the possible dependence of saccadic oscillations on a hypothesized membrane property of MLBNs: post-inhibitory rebound depolarization (leading to post-inhibitory rebound firing, PRF) [8], but that study did not deal with the effects of PRF on normal saccades. Furthermore, Kaneko and his colleagues have demonstrated the effect of lesions of the OPN region on the dynamical properties of saccades that can not be explained by previous models [9, 10]. The lesion results may reflect the effects of OPNs on activity in the MLBNs, because of the dense projections from the OPN region to that of MLBNs [11]. Here, we will suggest that biophysical properties of neurons may contribute to dynamical features of saccades. A preliminary version of this work has been presented elsewhere [12].

II. Membrane properties

A. Saccadic oscillations

Previously, it had been thought that saccadic oscillations occurred when inhibition was removed from the high gain negative feedback circuit (which had a feedback delay) [2]. Recently, Ramat et al. [8] have introduced the idea that a hypothetical property of MLBNs, post-inhibitory rebound depolarization, as well as brain stem inter-connections, may play a critical role in generating saccadic oscillations. They introduced detailed features of brain stem circuitry to distribute MLBNs into four populations: excitatory burst neurons (EBNs) and inhibitory burst neurons (IBNs) in left and right brain stem. Connections among MLBNs were based on the findings by Strassmann et al. [13, 14]: EBNs project to ipsilateral IBNs that project to contralateral EBNs and IBNs. In this model, offset of IBN causes rebound firing of contralateral EBNs and IBNs, whose offset of activity in turn causes rebound firing of IBNs and EBNs on the opposite side. Thus, oscillations occur. They have demonstrated that their model gives a better explanation for the mechanism for saccadic oscillations than the conventional one. A remarkable feature of their model is that the offset of OPNs may activate MLBNs, which can start saccadic oscillations. This raises the question of the effect of OPNs and the hypothetical post-

inhibitory rebound depolarization of MLBNs on normal saccades.

B. The effect of chemical lesions of OPN region

Kaneko demonstrated that peak velocity of saccades was decreased when the nucleus raphe interpositus, RIP, which contains OPNs, is damaged by injecting ibotenic acid [9]. Recently the same phenomenon was reproduced by muscimol injections into the same brain stem region [10]. RIP lesions significantly changed the dynamical features of saccades; there was a decrease in the peak velocity (by 70% at the maximum) and extended saccadic duration. However, other characteristics were normal, including saccadic accuracy and reaction time. A normal accuracy suggests that saccades are made under feedback control. This is consistent with classical findings [3, 15], and thus all saccadic models can explain this property. An extended saccadic duration is a natural consequence of a feedback controller with a slower eye velocity (perhaps due to a smaller drive signal), and thus is also explained by older models.

However, no model has yet been able to explain why RIP lesions cause saccadic slowing without a change in reaction time. A model for saccade generation proposed by Scudder [4] exhibits the decrease in peak velocity when OPNs are inactivated, but in this model the decrease in peak velocity must be accompanied by the shortening of reaction time of saccades [16]. If there is no shortening of reaction time, there would be no decrease in the saccadic velocity. In contrast, the lesion studies strongly suggest that the decrease in peak velocity is not correlated with a shortening of saccadic reaction times [10]. In most cases (10/14), changes in saccadic reaction time are not significant. Significant increases were seen in 3/14 cases, and a significant decrease was seen in only one case. Thus, the prediction from Scudder's model does not fit the data.

We need to find a mechanism for slowing down saccades that does not depend upon changes in saccadic reaction time. Remember that if MLBNs have the membrane property of post-inhibitory rebound depolarization, OPN offset will cause post-inhibitory rebound firing in MLBNs [8]. For a normal saccade, OPN offset occurs while MLBNs are also receiving the burst input from long lead burst neurons (LLBNs) from upstream regions. Thus, the rebound depolarization caused by the OPN offset will be added to this drive input. The effect of the post-inhibitory rebound depolarization will be to make the saccades faster than they would be with the LLBN input alone. This idea suggests a hypothetical mechanism underlying the effect of OPN lesions on saccadic speed. After OPN lesions, the additional drive, which would occur in response to OPN offset under normal condition, will be absent. Therefore, saccades will be slower. Of importance is that this hypothetical mechanism is independent of any changes in reaction time, because no specific changes in reaction time are required to generate saccadic slowing.

We still have to resolve the effect of OPN lesions on the reaction time of saccades. It has been suggested that the sources of input to MLBNs include LLBNs in the SC, pons and fastigial nuclei (FN) [17]. LLBNs in these areas commonly show activity lasting from long before the saccades in their "on direction" (referred to as build-up, prelude or sustained activity) followed by an intense burst component with a relatively long lead-time. Thus, the input to the MLBNs has the characteristics seen in these neurons, in particular, the prelude activity. The classical saccade models use the OPNs to inhibit the MLBNs before the saccade starts, thus preventing a response to prelude inputs, and preventing the eyes from drifting slowly before saccades. These classical models all predict a shorter reaction time after OPN lesion, because only the OPNs can block the prelude activity. Nonetheless, the experimental findings suggest that there must be another mechanism capable of blocking the prelude activity. There may be a second class of pause neurons that behave like OPNs and lies in different region from that of OPNs. However, this is not likely, because no report has been made of such neurons. Instead, we propose a new hypothesis: that this blocking mechanism may be achieved by a membrane property of MLBNs: a threshold for firing. Such thresholds obviously exist in neurons, because they do not fire until they are sufficiently depolarized. Thus, we are simply proposing that the threshold for firing may be a characteristic parameter of the neuron.

C. The model and simulation

Our new model of MLBNs now has two biophysical properties: post-inhibitory rebound depolarization and a threshold for firing. The schematic diagram of the model is illustrated in Fig. 1. This is an extension of the MLBN model used in the study by Ramat et al. [8]. The element that produces post-inhibitory rebound depolarization is implemented as a high pass filter, controlled by two parameters, Ga and Ta, that determine the magnitude and time constant of that rebound in membrane potential. The threshold is incorporated into the output function of MLBNs that transforms membrane state to firing rate. When the membrane state is below threshold, the output is zero. If it exceeds the threshold, the firing rate is determined by a soft-saturating non-linear function.

Saccades were simulated with a feedback control model incorporating the brain stem circuit introduced by Ramat et al. [8]. The new MLBN model was applied to all EBNs and IBNs. We assumed that LLBNs in the SC, pons and FN give inputs to MLBNs, as described above. The input to MLBNs was designed with the typical features of activities of neurons in these areas. For ipsilateral saccades, MLBNs receive an input that has a prelude activity that starts well before saccades, and an intense, long-lead, burst which

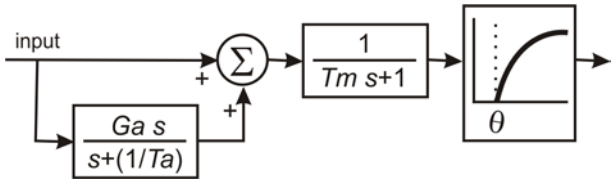

Fig.1. Schematic diagram of a medium-lead burst neuron. The model consists of a high pass filter that generates post-inhibitory rebound depolarization, a low pass filter, and an output function with a threshold θ that transforms membrane state to firing rate. Value of Tm was set to 0.001 s. Ga, Ta and θ were adjusted so that the model reproduced saccadic slowing after OPN lesion. In the example shown in Fig. 2, Ga, Ta and θ were set to 1, 0.010 s, and 180, respectively.

decays with the decrease in motor error down to below the threshold level of MLBNs. For contralateral saccades, MLBNs receive a late input whose onset is linked to saccade end. Activity of OPNs and the final common path is defined in the same manner as in [2] and in [6, 7], respectively.

Fig. 2 shows simulated 10 deg saccades before and after OPN lesion. To produce these saccades, we adjusted model parameters so that the saccades before and after OPN lesions satisfied the following criteria: 1) the peak velocity of saccades of 10 deg was about 450 deg/s when OPNs are normal and about 250 deg/s when OPNs are inactivated, which is similar to the actual values found in a monkey[10]; 2) the reaction time of these saccades is not different; 3) the latency of these saccades from the onset of the burst component in the LLBN input is 20 ms. The decrease in peak velocity after OPN lesion can be adjusted by manipulating the gain of rebound depolarization (Ga). The latency of saccades can be adjusted by the timing of offset of the OPNs when they are normal, or by the threshold in MLBNs when OPNs are inactivated. Thus, introducing the new MLBN model allows us to simulate saccadic behaviors that are consistent with experimental findings demonstrated by Kaneko and his colleagues [9, 10].

In the model, as stated in the previous section, the net drive signal produced by MLBNs is normally determined by the sum of the depolarization caused by OPN offset and the input from LLBNs. Thus, the rebound depolarization caused by OPN offset becomes an additional drive, increasing saccadic speed. Note that the rebound depolarization of contralateral MLBNs to the ongoing saccade is suppressed by inhibitory inputs to MLBNs (from IBNs on the opposite side), so that the membrane state can be kept small (under the threshold of neurons in most cases). After the lesion of OPNs, rebound depolarization is absent, resulting in slower saccades.

III. Discussion

Our hypothetical MLBN model includes two biological features, post-inhibitory rebound depolarization and a threshold, that are related to dynamical properties of

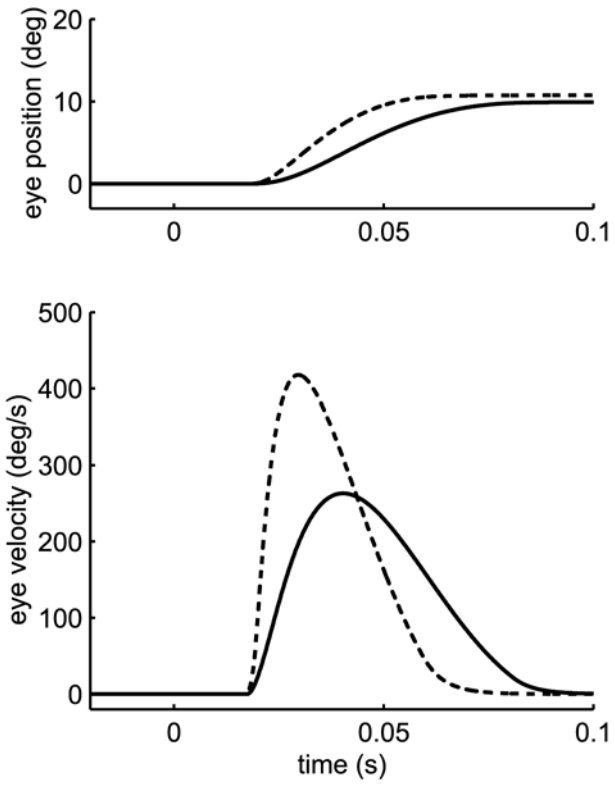

Fig.2 Comparison of simulated saccades before (broken lines) and after (continuous lines) OPN lesion of our model. Top and bottom show eye position and velocity, respectively. Time zero is the onset of burst component of inputs to MLBNs.

saccades, i.e. speed and latency in our model. So far, no study has been made to examine biophysical properties of MLBNs. Therefore, there is currently no evidence for the existence of the neuronal properties we hypothesize here, although both of the properties are common in neurons. The post-inhibitory rebound depolarization has been recognized in neurons in deep cerebeller nuclei [18] and in the medial vestibular nucleus in the brainstem [19]. Examining membrane properties of monkey MLBNs would test our hypothesis.

IV. Conclusion

In the classical scheme, the MLBNs are described as simple elements that have at most a single time constant and a firing rate saturation. Hence, they have no influence on saccade dynamics. Here, we have suggested the existence of more membrane properties of MLBNs that may contribute to the speed and latency of saccades. Thus, biophysical mechanisms in MLBNs, as well as the connections among neurons (i.e. circuits), may be important for dynamical properties of saccades.

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