A Mathematical Derivative Performed by Convergence of GABA and Glutamate in the Vestibular Periphery

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Closed-loop neuromuscular control systems rely upon the nervous system to generate, in real time, motor outputs in response to sensory inputs. This typically requires the central nervous system to perform calculations analogous to the fundamental operations of mathematical calculus. A classic example of this is the vestibular ocular reflex (VOR), in which angular-velocity encoding afferent signals are input to the brainstem, mathematically integrated by the central nervous system in real time, and output by motor neurons to control the angular position of the eyes. Mathematical differentiation by the nervous system has received less attention than integration, but differentiation is just as fundamental and perhaps much more ubiquitous. For example, step stimuli often evoke in single neurons an initial increase in firing rate followed by a period of adaptation. The initial increase in discharge rate and subsequent adaptation can be approximated in some cases by a fractional mathematical derivative. For the most rapidly adapting neurons, the fractional exponent approaches one and the neural response approaches a Dirac delta function. A mathematical derivative similar to the fractional model is present in the vestibular periphery, and is evidenced by responses of first-order semicircular canal afferent neurons that respond with discharge rates proportional to the rate of change of sensory hair cell intracellular voltage [1]. Current injection into afferents does not reproduce the adaptation evoked by synaptic inputs and therefore mathematical differentiation is not an intrinsic property of signal processing by afferent neuron ion channels. The contrast between hair cell voltage modulation and afferent responses implicates synaptic transmission and/or convergence of multiple inputs as the underlying source of the mathematical derivative. To investigate the convergence hypothesis, we injected afferent neurons intracellularly and found that neurons expressing mathematical differentiation always contacted hair cells that labeled positively for the neurotransmitter glutamate and, at the same time, contacted other hair cells that labeled positively for GABA [2]. Intra-arterial administration of CGP55845, a $GABA_B$ antagonist, eliminated the mathematical derivative thus showing the critical role of two-transmitter convergence in mathematical differentiation in this system. Furthermore, mathematical differentiation was shown not to be present in afferent responses when stimulating using sinusoids at frequencies above the $GABA_B$ G-protein delay time constant. A simple model incorporating the G-protein time delay and the convergence of excitatory and inhibitory inputs is sufficient to account for the data. Results demonstrate a simple mechanism utilized by the nervous system to perform low-frequency mathematical differentiation.

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References

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