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A model of a rapidly-adapting mechanosensitive current generated by a dorsal root ganglion neuron

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ABSTRACT

I propose a model that replicates the kinetics of a rapidly-adapting mechanosensitive current generated by a dorsal root ganglion (DRG) neuron. When the DRG neuron is mechanically stimulated, an ionic current called a mechanosensitive current flows across its membrane. The kinetics of mechanosensitive currents are broadly classified into three types; rapidly adapting (RA), intermediately adapting, and slowly adapting. The kinetics of RA mechanosensitive currents are particularly intriguing. An RA mechanosensitive current is initially evoked by and rapidly adapts to a mechanical stimulus, but can also respond to an additional stimulus. Furthermore, an antecedent stimulus immediately followed by an additional stimulus suppresses reactivation of the current. The features of the kinetics depend on the characteristics of the mechanotransducer channels. Physiologists have proposed three factors associated with mechanotransducer channels, invoking activation, adaptation, and inactivation. In the present study, these factors are incorporated into an RA mechanosensitive current model. Computer simulations verified that the proposed model replicates the kinetics of real RA DRG mechanosensitive currents. The mechanosensitive current elicited by successive pulse-form stimuli was predominantly desensitized by the inactivating factor. Both the inactivating and adapting factors were involved in desensitization of a double-decker stimulus. The reduction of the sensitivity with decreasing velocity of the stimulus was mainly controlled by the adapting factor.

1. Introduction

To understand how somatosensory information is processed in the brain, we must elucidate how this information is processed by cutaneous somatosensory receptors. Furthermore, an underlying cutaneous mechanoreceptor model is required to investigate somatosensory information processing using computer simulation. Mechanoreceptors convert mechanical stimulations to action potentials. The action potential is induced by mechanosensitive currents across the membrane of the mechanoreceptor. The characteristics of mechanoreceptors are governed by the kinetics of mechanosensitive currents. Hence, mechanoreceptors can be understood by clarifying the production mechanism of mechanosensitive currents. In the present study, I propose a model that reproduces rapidly-adapting mechanosensitive currents evoked by mechanical stimulation, as a first step toward understanding mechanosensory perception.

A mechanical stimulus is firstly processed by cutaneous mechanoreceptors. Mechanoreceptors detect mechanical stimulation through mechanosensitive channels on mechanosensory nerve endings that generate mechanosensitive currents in response to mechanical distortion. A mechanosensitive current is the integration of ionic flows through mechanosensitive channels. The kinetics of mechanosensitive currents evoked by mechanical stimulation are difficult to observe in detail [5,12,16]. Recently, new insights have been provided by Hao and Delmas [10] and Rugiero et al. [18,19], who investigated the kinetics of the mechanosensitive current of a cultured dorsal root ganglion (DRG) neuron using the patch clamp method. Mechanosensitive currents have been broadly classified as rapidly-adapting (RA), intermediately adapting, and slowly-adapting [6]. Among these, the kinetics of RA mechanosensitive currents are especially interesting. The RA mechanosensitive current initially responds to a mechanical stimulus, but rapidly adapts if the stimulus continues [6,10,12]. Although the receptor loses sensitivity to a long duration stimulus, it can respond to an additional stimulus [10,19]. However, the response to the additional stimulus is lower than that without the prior stimulus [5,10]. Furthermore, when the receptor receives two successive pulses of stimuli, reactivation by the second following pulse is depressed by the first pulse [10,19]. These current kinetics are known as desensitization. The features of RA mechanosensitive currents are governed by the characteristics of mechanotransducer channels, rather than by the cell type

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and physical properties of the membrane [1,5,10,17,19]. Mechanotransducer channels reside on the membrane of the mechanoreceptor and pass ionic currents when the receptor receives mechanical stimulation. The features of mechanosensitive current kinetics are considered to be produced by various factors of mechanotransducer channels, which remain poorly understood.

Mechanoreceptor models have been proposed by numerous researchers. Freeman and Jonson and Slavic and Bell developed equivalent circuit models [8,9,20], while Bell and Holmes proposed a model of pacinian corpuscles considering the physical interaction of laminae [2]. Simple models of Meissner corpuscles, a type of RA mechanoreceptor, were proposed by Looft et al. and Bensmaïa [3,14]. Their models reproduced the action potential of the receptor elicited by frequent stimulation. However, since the kinetics of mechanosensitive currents were then unknown, none of these models have included mechanosensitive ionic currents through mechanotransducer channels. The lack of experimental knowledge is attributed to the technical difficulty of investigating mechanosensitive currents [5,12,16].

The purpose of the present study is to model a rapidly-adapting mechanosensitive current in cultured DRG neurons, and demonstrate that the model can reproduce experimental results. Our model, which is based on the Hodgkin–Huxley conductance-based model, attempts to integrate some recent electrophysiological results and ideas proposed by physiologists. I assume that the mechanotransducer channels that generate mechanosensitive ionic flows are controlled by three factors; namely, by activating, adapting, and inactivating factors. Integrating these three factors into a mathematical model, resulted in successful reproductions of the experimental results of Hao and Delmas [10].

2. Model

This section presents our model of the rapidly-adapting mechanosensitive current in a cultured DRG neuron. The equivalent circuit of our model is described in Fig. 1(A). Our model is based on the channel current model of Hodgkin and Huxley [11]. I regard the mechanosensitive current as ionic currents through mechanotransducer channels. In the Hodgkin–Huxley model, whole ionic currents through a membrane consist of currents through all ion channels in the membrane, each controlled by the conductance of its channel.

The mechanosensitive current across the membrane through all of its mechanotransducer channels at time t, $I(t,s)$, is given by

$$I(t,s) = I_C(t) + \sum_{k=1}^{N} I_k(t,s), \tag{1}$$

when $I_C(t)$ is the capacitive current, $I_k(t,s)$ is the current through the kth mechanosensitive cation channel, and N is the number of mechanosensitive cation channels. The channels open in response to a mechanical stimulus s, here regarded as the movement of a mechanical probe toward a mechanoreceptor. The capacitive current $I_C(t)$ is defined by $I_C(t) = dQ/dt$. The charge Q is defined by $Q = CV$, where C is the membrane capacitance and V is the voltage across the membrane. Since the voltage is constant in the voltage clamp method, we have $I_C = CdV/dt = 0$, and Eq. (1) reduces to

$$I(t,s) = \sum_{k=1}^{N} I_k(t,s). \tag{2}$$

As mentioned above, the mechanosensitive current $I(t,s)$ sums the currents passing through the mechanotransducer channels. In the present study, all transducer channels are cation channels, because cations are passed non-selectively by real mechanotransducer channels [4,6,7,10,13,15,16]. The ionic current contributed by the kth cation channel, $I_k(t,s)$, is calculated from Ohm's law as $I_k(t,s) = g_k(t,s)(V - E_k)$, where E_k is the reversal potential and $g_k(t,s)$ is the conductance of the kth channel. Since the objective is to reproduce the results under voltage clamp, $V - E_k$ is assumed constant in the model and $V - E_k$ is set to V_C, where $V_C = 60$ mV [10]. If the channels open when a receptor receives a mechanical stimulus, the kth ionic current flows across the membrane with

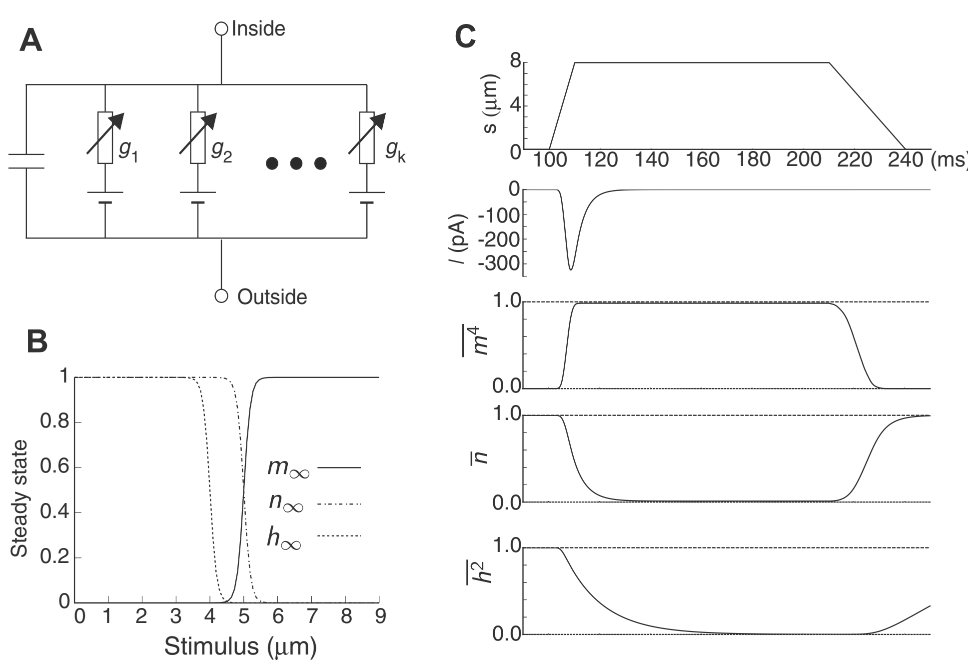

Fig. 1. (A) Equivalent circuit of the mechanoreceptor model. g_k denotes the conductance of the kth mechanotransducer channel. (B) The stimulus-dependent functions of our model. Shown are $m_\infty(s)$, $n_\infty(s)$, and $h_\infty(s)$, the steady-state levels of activating, adapting, and inactivating factors of the conductance, respectively. (C) Time traces of the variables. A trapezoidal mechanical stimulus $s(t)$ of 100 ms duration was applied (top trace). $\overline{m^4}$, $\bar{n}$, $\overline{h^2}$ are the averages of the activating, adapting, and inactivating factors, respectively, of the mechanosensitive channels.