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Simulation analysis of the effects of the simultaneous release of quanta of acetylcholine on the endplate current at the neuromuscular junction

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Abstract

Arrival of an action potential to a nerve terminal at the neuromuscular junction induces the release of a few hundred quanta of acetylcholine (ACh) into the synaptic cleft, resulting in depolarization of the muscle cell which is observed as the endplate current (EPC). The release of each quantum of ACh invokes the miniature endplate current (MEPC), so that an EPC could be generated by summation of the MEPCs both in time during evolution of the EPC and in space for a certain area of the post-synaptic membrane. In this study, a mathematical model for EPC generation is developed as a reaction–diffusion system (RD system) which represents the dynamic behavior of ACh in the chemical transmission process with the simultaneous quantum release of ACh. The RD system for ACh is mathematically expressed by a two-dimensional diffusion equation with nonlinear reaction terms due to the rate processes for acetylcholinesterase (AChE) and ACh receptor (AChR). Numerical solution of the governing equation with the method of lines and the Gear method yields temporal changes in relative concentrations of the open channel form of AChR which is assumed to be equivalent to the EPC. Analysis of the behavior of the RD system with respect to the various distances between the release sites of ACh on the pre-synaptic membrane demonstrates that the amplitude of EPC is quite sensitive to the distances around 0.5 μm, but independent of the values of the diffusion coefficient of ACh in the synaptic cleft.

Keywords: Endplate current; Reaction–diffusion system; Compartment model; Computer simulation

1. Introduction

A two-dimensional compartment model for the dynamic behavior of acetylcholine (ACh), a typical neurotransmitter, in spontaneous generation of the miniature endplate current (MEPC) at the neuromuscular junction has been proposed [8] to analyze the transient process of the synaptic transmission. The

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model is formulated in a polar coordinate system of the radial and transverse axes to express the respective diffusion process of ACh in the axis-symmetrical disc which represents a certain effective space in the synaptic cleft for the generation of MEPC. It is revealed from the analysis with this model that the radial diffusion process of ACh has more distinctive effects on spontaneous generation of the MEPC than the transverse diffusion process, so that even the homogeneous state is apparently allowed in the transverse direction. This model is also applied to examine the functional significance of the specific structures of the junctional folds [5] and of the synaptic vesicles [7] at the neuromuscular junction. The neurotransmitter release mechanism is further analyzed with the model through evaluation of the characteristic parameters of MEPC [6].

In this study, the compartment model is modified to delineate the process for the generation of the endplate current (EPC) comprised of a number of MEPCs in response to the respective quantal release of ACh. Instead of the polar coordinate system, the Cartesian coordinate system with the two orthogonal axes in a square plate of the synaptic cleft is employed to represent the dynamic behavior of multiple MEPCs. Diffusion of ACh takes place in the longitudinal directions and the homogeneous concentration of ACh is assumed in the transverse direction. The effects of the density of the quantal release of ACh on generation of the EPC are analyzed with the model, revealing that the change in the distance between the release sites of ACh on the pre-synaptic membrane has significant effects on the amplitude of EPC regardless of the values of the diffusion coefficient of ACh in the synaptic cleft.

2. Construction of the model

2.1. Mechanisms for ACh release and transmission in the synaptic cleft

An action potential arrives at the nerve terminal, inducing the release of a few hundred quanta of ACh into the synaptic cleft. The ACh molecules released diffuse in the synaptic cleft, undergoing hydrolysis by acetylcholinesterase (AChE), and binding with ACh receptor (AChR) to alter the ionic permeability of the muscle cell membrane. This change results in depolarization of the muscle cell which is observed as the EPC. The EPC could be considered as the sum of the MEPCs invoked by respective release of a quantum of ACh both in time during evolution of the EPC and in space for a certain area of the post-synaptic membrane. Though three dimensions in space are required to represent the summation of MEPC in time and in space, the assumption of simultaneous release of all quanta of ACh allows formulation of the EPC generation process in the two-dimensional compartment model with Cartesian coordinate system.

In a reaction–diffusion system (RD system) as illustrated in Fig. 1, the ACh concentration $A(x, y, t)$ is assumed to vary with time t and point (x, y) in a space of square plate of the synaptic cleft with the side length $2L$ and height w. The homogeneous concentration of ACh in the transverse direction is assumed, and this is justified with the analysis of the dynamic behavior of ACh previously described [8]. Instead of the polar coordinate system in an axis-symmetrical disc, which has been used to formulate the RD system of MEPC, the model is constructed with the Cartesian coordinate system in a space of square plate which is suitable to fill up the space of the synaptic cleft with the multiple quantal releases of ACh corresponding to the EPC.

The ACh molecules are released into the synaptic cleft from the narrow pore formed by the fusion process of a synaptic vesicle with the pre-synaptic membrane. After the localized influx from a synaptic vesicle through a square area with the side length of $2d$ on the pre-synaptic membrane, the ACh molecules