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SYNAPTIC TRANSMISSION: A MODEL ON THE FORMATION OF END-PLATE POTENTIAL AND A STUDY ON SIMULATION

Levent ÖZBEK, Çağri TEMUÇIN, Bülent CENGIZ and Fikri ÖZTÜRK

ABSTRACT. In this study, the emergences of postsynaptic action potentials are investigated using simulation study which is depended on the statistical model of acetylcholine-quantal (Ach) release theory at motor end-plate. It is supposed that the end-plate potentials (EPP) are sum of miniature end-plate potentials (MEPP) which are released as quantal and random in number (N). By the hypothesis that N number has a Poisson and MEPPs have a Gaussian distribution, EPPs are obtained by simulating distributions parameters. Our study suggests that the simulation of the EPPs are a convenient tool in understanding both physiological process of synaptic transmission and pathological process of neuromuscular junction.

1. INTRODUCTION

The functions of multicellular living beings demand communication among cells. A simulation study on a model regarding the formation of end-plate potential which is an important subheading of neurophysiology has been made.

Any kind of change in inner or outer environment is transformed into electrical signals in specialized cells and transmitted through neurons to the brain where it is perceived, interpreted, and preserved. Commands given by the brain to the executive organs such as muscles and glands are also transmitted as potential changes in the nerve cells.

Resting membrane potential has a characteristic value for each cell. When the nerve and membrane cells are stimulated by a proper stimulus, a temporary change happens in the membrane potential. If the value exceeds a critical level, a quick

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transmission of information through the potential changes which may spread along the membrane is conducted among the organs.

Cells called *nerve cells* or *neurons* feature in transmission of information in the nervous system. The touch area in which the information exchange is conducted between two neurons is called *synapse [1]*. The information gathered from other neurons by the dendrites or synaptic connections of a neuron is transmitted as potential changes through its axone to the nerve endings. It may also be transmitted from nerve endings to other cells synaptically.

The resting state of nerve and membrane resembles a polarized condenser which has a positive charge outside, a negative charge inside and a good insulator originating from lipid (fat) bilayer at the center. Under the influence of a proper stimulus, the condenser is likely to discharge and may even depolarize for a short amount of time. After this potential change that happens in about 1 millisecond in a particular area of the membrane, the potential change continues spreading along while the membrane is turning back to the resting state. This potential change which is the fundamental unit of the information transmitted through the tendon is called *the action potential*. These potential changes may be monitored and recorded with electrical measurement and observation tools.

If the cells are too far away from each other, the transmission of information takes place by chemical factors. Transfer of information between neighbor nerve cells or between a neighbor nerve cell and a membrane cell is called *synaptic transmission*; specialized regions in which the communication between neighbor cells take place are called *synapses*. The cell called *sender* and *presynaptic cell* and the receiver *postsynaptic cell* get considerably closer to each other in these intersection points.
There are little saccules at the endings of axones. These saccules contain neurotransmitters which play an active role in the synaptic transition. When the action potential reaches the end of a nerve, molecules of neurotransmitters are released from these saccules to synaptic gap. Some of the molecules moving by the diffusion in the intercellular liquid that fills the synaptic gap are able to canalise through ionic channels (or some channels are likely to be closed) in the postsynaptic membrane. As a result of the changes of conductibility and permeability, potential changes happen in the postsynaptic membrane. If the potential change that is generally called postsynaptic potential reaches a critical value, an action potential spreading through the membrane is likely to develop.

When a stimulation spreading through a motor neuron reaches the end of a nerve, it is able to be transferred to the muscle fibre through the synaptic transmission in the neuromuscular junctions. Neuromuscular junctions are also known as end-plates. The basic chemical substance in-between the neuromuscular junction is acetylcoline (ACh). There are plenty of ACh saccules at the endings of motor neurons; in suitable conditions, they combine with the membrane and release ACh molecules they contain to the synaptic gap. While some of the released ACh molecules move away from the gap by the diffusion, some of them combine with the receptors in the postsynaptic membrane causing a local potential change. If this potential change named *End-Plate Potential (EPP)* exceeds a critical level, an action potential emerges.

The ACh saccules found at the endings of nerves are occasionally able to develop and discharge by itself, causing little amounts of depolarization about 0.5 mV in the end plate. As a result of examining these potential fluctuations named *miniature late plate potentials (MEPP)*, it is understood that the molecules of acetylcoline are oscillated in little packages or *quantums* and a normal *EPP* emerges as a result of the simultaneous oscillation of many individual quantums at the presynaptic ending. Findings that Dale and his colleagues got in 1936 indicated that the transmission of the signal from the nerves to the muscles was taking place through the molecules of acetylcholine (ACh) [2]. Studies made by Katz and Fatt in 1951 provided an opportunity to understand the mechanism of this phenomenon [3]. These researchers determined that there was a spontaneous transmission per second in a frog's neuromuscular junction. They observed that these spontaneous potentials were much smaller than potential amplitudes which are obtained through nerve stimulation. The potentials that emerge through nerve stimulation are called *End-Plate Potentials (EPPs)* and the smaller potentials that emerge spontaneously are called Miniature End-Plate Potentials (MEPPs).

According to the Quantum Hypothesis put forward by Castillo and Catz in 1955 [4], EPPs represents the total amount of MEPPs (Catz received the Nobel prize in 1970 at University College London). This means that the synaptic transmission comprises of the reproduction and accumulation of a particular amount of little packages. It is observed with an electron microscope that saccules 500 angstrom in diameter were existing almost simultaneously. Afterwards, it is determined that these saccules were containing ACh. Thus, the quantal characteristic of the synaptic transmission has been revealed with the evidences.

This paper is organized as follows: In Section 2, a stochastic model for synaptic transmission proposed by [5] and [6] are summarized. In Section 3, simulation results are presented. Section 4 concludes.

2. Model

A simple stochastic model has been put forward to test the quantum hypothesis. The model is grounded on the anatomic finding that there were oscillation areas of transmitters which are distinguishable from each other. According to this hypothesis, *arbitrary* number of oscillation areas activate when the stimulus reaches the junction. It is a well-accepted (also tested with empirical observations) fact that the *number (n)* of the oscillation areas which are activated within a stimulus had the features of the Poisson distribution. MEPPs independent from each other take place in the postsynaptic area by the activation of these different oscillation areas.

Experimental data has shown that the amplitude of these MEPPs was distributed normally [7]. The experimental data also shows that the EPPs emerge in the postsynaptic area may be described as the total temporal and spatial amount of MEPPs. In case the amplitude of EPPs reaches a level that depolarizes a membrane over a particular threshold value, an action potential emerges. This potential spreads through the voltage-gated sodium channels in the membrane along the muscle fibre and causes muscle contraction. The amplitude of the EPPs which emerge following a presynaptic stimulation normally equals to four times the threshold value (safety factor). The mathematical expression for the hypothesis is as follows. Simple stochastic model was advanced which could test the quantum hypothesis. Based on the anatomical evidence, it was supposed that there were physically distinguishable transmitter release sites. When a nerve impulse invades the junction, a random number (say N) of these sites are activated. Let the contributions from the various release sites be independent and identically distributed random variables X_k so that the total response is

$$V = X_1 + X_2 + ... + X_N \tag{1}$$

Based on experimentation, a reasonable approximation is that X_k's are normally distributed

$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2}, -\infty < x < \infty, -\infty < \mu < \infty, \sigma^2 > 0 \qquad (2)$$

with mean μ and variance σ^2. The natural choice for N is that of a binomial random variable, but in the original model it was assumed to be Poisson (λ)

$$f(N = n) = \frac{e^{-\lambda}\lambda^n}{n!}, \quad n = 0,1,2, \ldots \qquad (3)$$

$E(N) = \lambda$ and $Var(N) = \lambda$, so the amplitude of the EPP becomes compound Poisson. The density of V is given by

$$f(v) = e^{-\lambda}\left[\delta(v) + \frac{1}{\sqrt{2\pi\sigma^2}} \sum_{k=1}^{\infty} \frac{\lambda^k}{k!\sqrt{k}}\right] \exp\left(\frac{-(v-k\mu)^2}{2k\sigma^2}\right) \qquad (4)$$

where $\lambda = E(N)$ (The details of the proof see Tuckwell, 1994 and Tuckwell, 1995). The mean and variance of V are

$$E(V) = \lambda\mu$$
$$Var(V) = \lambda(\mu^2 + \sigma^2)$$

The excellent fit of $f(v)$ to experimental distributions of some EPP amplitudes provided impressive evidence to support the quantum hypothesis (see Martin, 1977).

3. The Simulation for the Emergence of the End-Plate Potential

Valuing the variables in the proposed model differently, two separate simulation studies have been made.

In order to generate numbers from the density function given in Equality 4, the corresponding distribution function and its reverse form must be determined. Due to the fact that this distribution function is not easily found, Equality 1 is used to generate numbers from the distribution which is relevant to the density function given in Equality 4. Firstly, parameter λ is determined and then, the N number is generated from the Poisson distribution (Equality 3) with regard to the parameter. Afterwards, N amount of number is generated from the normal distribution

(Equation 2) in μ and σ^2 parameters set and the N amounts of numbers are added together. Same process is repeated m times and the histogram for the numbers are drawn. m was assumed as being equal to 5000 in the simulation studies made. MATLAB application has been used for the studies.

3.1 First Simulation

The simulation was generated from the Poisson distribution with an average of 2.4 N value. X_k 's were generated from the normal distribution with 0.4 mean and 0.1 standard deviation. The EPP mean was found to be 0.9601 and the standard deviation was 0.6399. The EPP minimum was found to be 0 and the maximum was 5.7179. In these circumstances, the histogram for the obtained EPPs is given Figure

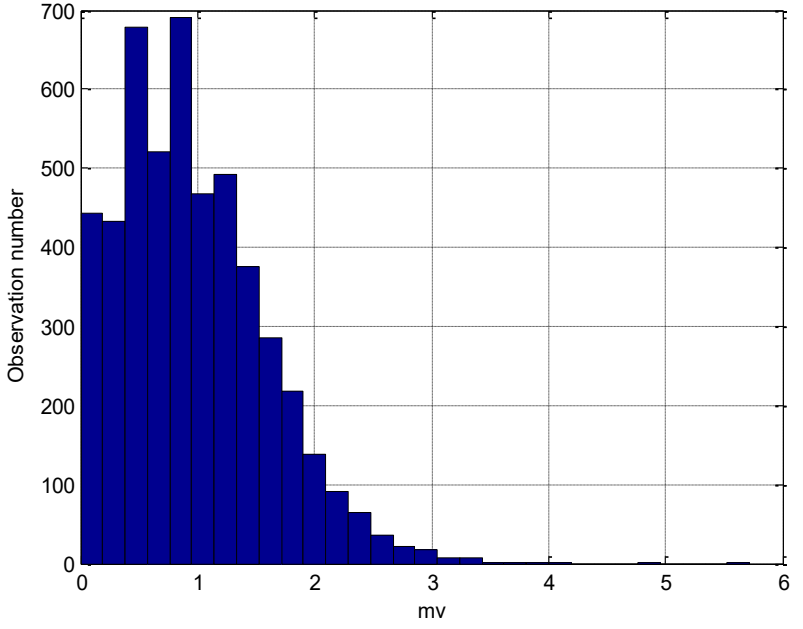

Figure 1: EPP simulation λ = 2.4, N (0.4, 0.1).

3.2 Second Simulation

It is shown that the amplitudes of MEPP decreased in *myasthenia gravis (MG)* disease. Providing that the N number is same within the simulation for the dysfunction of postsynaptic neuromuscular junction, the X_k averages which represent the average amplitude for the MEPPs are decreased. X_k were generated from the normal distribution with 0.2 average and 0.1 standard deviation. The EPP average was found to be 0.4827 and the standard deviation was 0.3488. The EPP minimum was found to be -0.1341 and the maximum was 2.7074. In these circumstances, the histogram for the obtained EPPs is given by Figure 2.

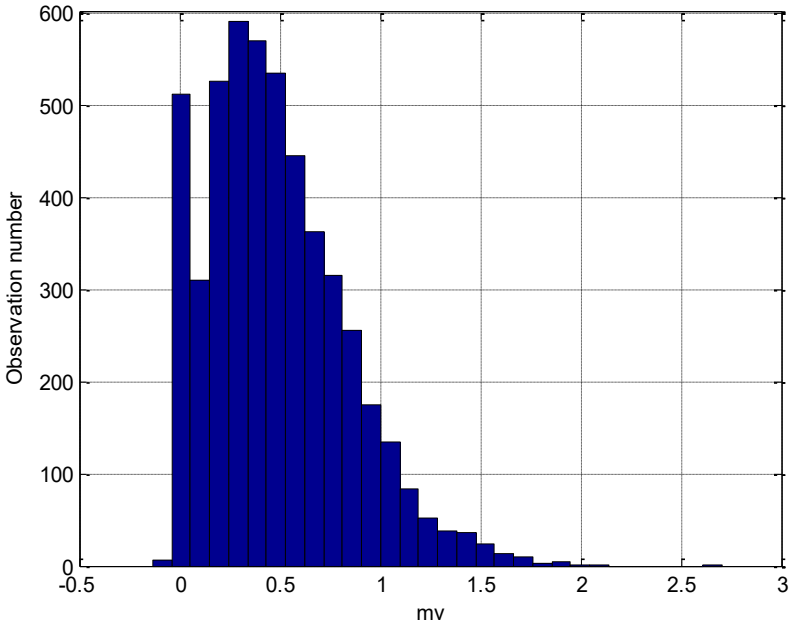

Figure 2: EPP simulation $\lambda = 2.4$, N (0.2, 0.1).

As one may see, there is a decrease in the amplitude of the EPPs in the simulation for the MG physiopathology, leading the safety factor to decrease too. These changes predicted by the simulation are coherent with the clinical and electrophysiological observations.

4. Conclusion

This study aimed to research the emergence of the postsynaptic action potentials using the simulation study based on the statistical model in the theory of acetylcholine-quantal (Ach) release at motor end-plate. End-plate potentials (EPP) have been assumed as amounting to the total for numerically (N) quantal and randomly-released miniature end-plate potentials (MEPP). EPPs have been obtained by simulating the distribution parameters based on the hypothesis that N number was in Poisson and MEPPs were in Gaussian distribution. The results of this study have suggested that the simulation of EPPs might be the appropriate means by which both the neuropathic transmission and the neuromuscular resultant's physiopathological process are understood.

By including the other variables such as the stimulation frequency, the ambient temperature, the width of the synaptic gap, the number of the presynaptic saccules, and the physiology of calcium channels in the further researches, much more realistic models and simulation studies may be made.

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Current Address: Levent Özbek, Ankara University, Faculty of Sciences, Department of Statistics, Ankara, Turkey
E-mail: ozbek@science.ankara.edu.tr
ORCID: https://orcid.org/0000-0003-1018-3114

Current Address: Çağrı Temuçin, Hacettepe University, Medical Faculty, Department of Neurology, Ankara, Turkey
E-mail: ctemucin@hacettepe.edu.tr
ORCID: https://orcid.org/0000-0003-0127-6861
Current Address: Bülent Cengiz, Gazi University, Medical Faculty, Department of Neurology, Ankara, Turkey
E-mail: bcengiz@gazi.edu.tr
ORCID: https://orcid.org/0000-0002-1688-9516

Current Address: Fikri Öztürk, Ankara University, Faculty of Sciences, Department of Statistics, Ankara, Turkey
E-mail: ozturkf@ankara.edu.tr
ORCID: https://orcid.org/ 0000-0002-7175-7372