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Impact of substance P on the correlation of spike train evoked by electro acupuncture

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ABSTRACT

Substance P (SP) participates in the neural signal transmission evoked by electro-acupuncture (EA). This paper investigates the impact of SP on the correlation of spike train in the median nerve evoked by EA at 'Neiguan' acupoint (PC6). It shows that the spiking rate and interspike interval (ISI) distribution change obviously after inhibiting SP. This variation of spiking activity indicates that SP affects the temporal structure of spike train through modulating the action potential on median nerve filaments. Furtherly, the correlation coefficient and scaling exponent are considered to measure the correlation of spike train. Scaled Windowed Variance (SWV) method is applied to calculate scaling exponent which quantifies the long-range correlation of the neural electrical signals. It is found that the correlation coefficients of ISI increase after inhibiting SP released. In addition, the scaling exponents of neuronal spike train have significant differences between before and after inhibiting SP. These findings demonstrate that SP has an influence on the long-range correlation of spike train. Our results indicate that SP may play an important role in EA-induced neural spiking and encoding.

1. Introduction

Acupuncture is a widely accepted treatment in traditional Chinese medicine. A great number of long-range clinical practices have proved acupuncture effects, such as modulating of heart rate [1], blood pressure [2], relaxing muscle pain [3] and so on. However, the mechanism of information transmission evoked by acupuncture still has not been understood explicitly. Many research works indicate that applying Electro-Acupuncture (EA) as an electrical stimulation to an acupoint can produce the corresponding neuronal electrical signals, and then the information is transmitted through nervous fibers to spinal cord and senior regions [4,5]. Characterizing the temporal structure of acupuncture-evoked spike series is conductive to reveal the mechanism of acupuncture effects.

Recently, more and more efforts have been made to characterize the temporal structure of acupuncture-evoked spike train, such as spiking rate, spike distribution and correlation analysis [6,8–11]. Long-range correlation is one of the most typical temporal structures of time series, which manifests as a statistical self-similarity in multiple time scales [7]. It is reported that both spontaneous [8,9] and acupuncture induced [10,11] neuronal signal exhibit long-range correlation. In particular, the existence of long-range correlation in acupuncture-evoked spike activity provides the information about the working mechanism of acupuncture [10,11]. Accordingly, this paper focuses on the correlation of the spike train evoked by EA.

Besides, investigations increasingly focus on the contribution of the neuropeptide in the neural signal transmission during acupuncture [12,13]. Substance P (SP) is one of the most important neuropeptide, which widely lives in nerve filaments [14], spinal cord [15], hypothalamus [16] and other areas. SP released in the spinal cord [17] and nociceptors [18] participates in the neural signal transmission via binding to neurokinin 1 (NK1) receptor [19]. In recent years, a great number of scientific literatures reveal a closer relationship between SP and acupuncture effect [20–25]. During acupuncture, SP is released by nerve terminal [20], which leads to fiber exciting and signal transmission [21,22]. It is interesting that SP not only contributes to the pain transmission [23,24], but also plays a positive role in EA analgesia effect [25]. Lee et al. and Jung et al. suggest that acupuncture plays a therapeutic role in pain model via inhibiting the expression of SP [23,24]. Bian et al. reveal that blocking the SP receptor suppress medium and high frequency EA analgesia effect [25]. These literatures show the complexity of the impact of SP on the acupuncture. The study on the impact of SP on acupuncture-evoked spiking activity is beneficial to uncover

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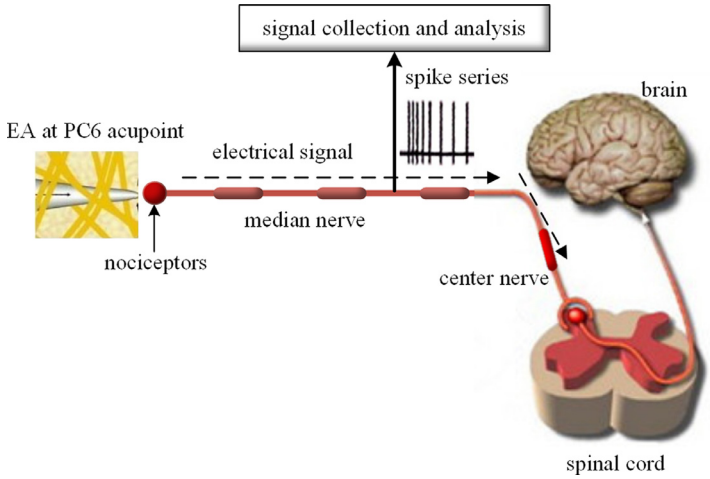

Fig. 1. The information pathway of the EA induced spike. When the body is stimulated by acupuncture at 'Neiguan' acupoint (PC6), EA causes a pain to nociceptors, which release several chemical factors to bring a depolarization to median nerve membrane potential. The electrical signal can be transmitted to spinal cord along the peripheral nerves and center nerves. We collect the spike series in median nerve for analyzing.

the neural mechanism of acupuncture. However, this issue is still in the exploratory stage. In particular, there is a lack of study about the relationship between SP and the long-range correlation of electrical signal evoked by acupuncture.

In this paper, the neural activities of median nerve fiber evoked by EA at 'Neiguan' acupoint (PC6) are recorded. We observe the long-range correlation of the spike trains both before and after the administration of spantide or Phosphate Buffer Solution (PBS) to PC6 area. Correlation coefficients and Scaled Windowed Variance (SWV) method are used for evaluating the correlation of spike train. In addition, the distribution of interspike interval (ISI) is applied to observe the temporal structure of spike train. The spiking rate is calculated for estimating the change of the structure.

The rest of this paper is organized as follows. The acupuncture experimental paradigm and data analysis methods are described in Section 2. In Section 3, the correlation coefficient and spiking rate variation are applied to characterize the spike train. The scaling exponent measures the impact of SP on long-range correlation of EA-induced spike train. Finally, the conclusion and discussion are drawn in Section 4.

2. Methods

2.1. Surgical preparation and data acquisition

Experiments were approved by Animal Ethics Committee of Tianjin University of Traditional Chinese Medicine in PR China. Ten healthy adult rabbits (approximate weight 2–2.5 kg) were divided into two groups, experimental group and control group. Prior to surgical procedure, each rabbit was anesthetized deeply by 20% ethyl carbamate (10 ml/kg). After slicing the skin of rabbit along median line of the inside forelimb near armpit, the median nerve was exposed. The silver electrode (diameter, 0.1 mm) was connected to median nerve filaments which were exposed by separating nerve sheath from the median nerve. The periodical electrical acupuncture (2Hz) was taken at PC6 of the rabbits in both group. Fig. 1 showed the pathway of electrical signal induced by EA.

The data detected by silver electrode were recorded by MP150 (BIOPAC, USA) equipment and then filtered (100 Hz to 3 kHz bandwidth) for off-line analyses. The sampling frequency was 40kHz. Spantide, a non-peptide SP antagonist [26–28], was used to inhibit the expression of SP. PBS is a common buffer solution, which was used for dissolving the spantide. In order to exclude the influences of buffer solution and experimental environment, we injected with PBS to rabbits in the control group. The recording procedure and the recorded data were showed in Fig. 2.

Before each experimental protocol, a 5min period was allowed to confirm the stability of the recording. The neuron activities were recorded according to following steps: (1) the state during the first time periodic EA (DEA1): the spike series were recorded for about 2min before injecting anything to PC6 in both groups. (2) the state during the second time periodic EA (DEA2): the spike series were recorded for another 2min after injecting spantide (50 μ1) to PC6 of all rabbits in the experimental group, PBS (50 μ1) to rabbits PC6 in the control group. The EA frequency was 2Hz.

2.2. Data preprocessing

The neural electrical signals evoked by EA are disturbed by artifacts which will largely mislead our analysis of the spike series. Accordingly, the Stimulation Artifact Removal Graphical Environment (SARGE) framework [29] was used to remove artifacts of the recording data. After removing the artifacts, the wave-clus package [30] is applied to detect the spikes. The spike threshold is set as 4 times the estimated standard deviation of the noise in the signal. Then we use wavelet transform to obtain the spike timing through extracting character of the spike shapes. To avoid conflicting results among various types of spike, the wave-clus is only used for detecting spikes.

2.3. ISI correlation analysis

ISI refers to the interval between two adjacent spike times in sequence of action potentials, which contains a wealth of neural encoding information [31]. Therefore the spike train can be converted into a series of ISIs (Δt_1, Δt_2, ..., Δt_N) for analysis. To analyze the temporal correlation of ISI sequence, we compute the correlation coefficient (CC) defined as [32]:

$$CC = CORR/VAR \tag{1}$$

where VAR is the variance of ISIs. Additionally, $CORR$ is the correlation covariance between two adjacent ISIs (Δt_i and Δt_{i+1}), which is given by:

$$CORR = \sum_{i=1}^{N-1} (\Delta t_i - \overline{\Delta t}) \times (\Delta t_{i+1} - \overline{\Delta t})/(N-1) \tag{2}$$

where $\overline{\Delta t}$ is the mean value of ISIs. N is the length of ISI sequence. It should be noted that the value of CC is between -1 and 1. $CC =$