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Detailed spectral profile analysis of penicillin-induced epileptiform activity in anesthetized rats

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Summary Penicillin model is a widely used experimental model for epilepsy research. In the present study we aimed to portray a detailed spectral analysis of penicillin-induced epileptiform activity in comparison with basal brain activity in anesthetized Wistar rats. Male Wistar rats were anesthetized with i.p. urethane and connected to an electrocorticogram setup. After a short period of basal activity recording, epileptic focus was induced by injecting 400 IU/2 μl penicillin-G potassium into the left lateral ventricle while the cortical activity was continuously recorded. Basal activity, latent period and the penicillin-induced epileptiform activity periods were then analyzed using both conventional methods and spectral analysis. Spectral analyses were conducted by dividing the whole spectrum into different frequency bands including delta, theta (slow and fast), alpha—sigma, beta (1 and 2) and gamma (1 and 2) bands. Our results show that the most affected frequency bands were delta, theta, beta-2 and gamma-2 bands during the epileptiform activity and there were marked differences in terms of spectral densities between three investigated episodes (basal activity, latent period and epileptiform activity). Our results may help to analyze novel data obtained using similar experimental models and the simple analysis method described here can be used in similar studies to investigate the basic neuronal mechanism of this or other types of experimental epilepsies.
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Introduction

Clinical experience has indicated that high systemic doses of penicillin in humans can produce myoclonus, generalized tonic-clonic seizures and encephalopathy (Fossieck and Parker, 1974). In addition, it is well known that intracortically or systemically administered penicillin results in a prominent epileptiform activity both electrophysiologically

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and behaviorally in laboratory animals (Chen et al., 1986; Fisher, 1989). After these observations the penicillin-induced epilepsy (PIE) became an experimental model in the study of epileptiform activity (Fisher, 1989). A general Pubmed medline search performed in 5th May, 2008 resulted in 1195 research articles using ''penicillin'' and ''epilepsy'' keywords, while a search using ''penicillin-induced epilepsy'' string gives 962 article in results.

Electrophysiological studies on PIE are basically focused on the latency to the beginning of epileptiform discharges and on both the mean amplitude and the number of epileptiform discharges (spikes) along certain time windows (Marangoz et al., 1994; Bagirici et al., 1999, 2001; Bosnak et al., 2007; Bostanci and Bagirici, 2007; Yildirim and Marangoz, 2007). For most circumstances these approaches can give a limited picture about the mechanism and pharmacology of the experimental plan and some satisfying conclusions can be drawn from such analysis. This conventional approach is generally quite easy to apply, especially using the modern computer-assisted electrophysiological recording or data analysis systems. But some aspects of neural activity which can be detected by other means may remain hidden when such conventional analysis techniques are used, as we will discuss later.

Another widely used approach for analyzing electrophysiological signals is to convert the time-dependent signals into its frequency domain using a number of algorithms including Fast Fourier Transform (FFT) or Wavelet analysis (Akin, 2002). Such approaches are now widely used in different areas of quantitative signal processing especially as a result of widespread availability of computer power for large data sets. The main idea underlying such methods is to extract as much information as possible from a given time-varying signal via observing its specific frequency components. In some instances, analyzing a signal using such algorithms may reveal some hidden changes which may not be clearly visible during visual inspection or spike/latency analysis.

The use of spectral analysis in the area of epilepsy research is rather limited except some clinical studies (Muthuswamy and Thakor, 1998; Hughes and John, 1999; Van der Hiele et al., 2007). Especially in the field of PIE, there are only little data on the spectral profile and the time—frequency characteristics of epileptiform activity induced by penicillin (He et al., 1990; Timofeeva and Gordon, 2001; Feng et al., 2004).

The main focus of the presented study is to obtain a detailed spectral analysis of the basal brain activity monitored during anesthesia, the latent period and spike-wave activity periods which is generally observed after penicillin administration in anesthetized rats and to discuss our findings which might be of interest for the researchers studying in this area.

Materials and methods

Animals

Four months old male Wistar rats weighing 198 ± 13.05 g were used in this study. Animals were kept in heat-regulated rooms, on a 12-h day/12-h night cycle, and given as much food and water as needed. All experimental procedures were carried out according to the guidelines of European Community Council for experimental animal care.

Surgical procedure

Animals anesthetized with urethane (1.2 g/kg; i.p.) and the scalp covering the skull has been cut with a rostro-caudal incision of 3—4 cm long. Skull bone covering the left upper surface of the brain was removed by gradual thinning with a dental drill. After complete removal of the left side of the skull, dura mater was removed using microscissors and the animal was fixed on a stereotaxic instrument (Harvard, USA). Body temperatures of the animals were continuously monitored and kept constant at a temperature of 37 ± 0.5 °C using a homoeothermic blanket system throughout the study (Harvard Homoeothermic Blanket System).

Experimental design

Two Ag—AgCl ball electrodes were placed over the left somatomotor cortex (electrode coordinates: first electrode; 2 mm lateral to sagittal suture and 1 mm anterior to bregma; second electrode; 2 mm lateral to sagittal suture 5 mm posterior to bregma). Electrodes were connected to a digital data-acquisition system (Powerlab/4SP, AD Instruments, Australia) and electrocorticograms (ECoGs) were recorded digitally to a computer hard drive using 1 kHz sampling resolution and 0.1—100 Hz filter. In order to induce an epileptic focus, each animal was received an intracerebroventricular (i.c.v.) injection of crystallized penicillin-G potassium (400 IU/2 μl) using a Hamilton microinjector through an injection point located 1.5 mm anterior, 2 mm lateral to the bregma, with a depth of 4.2 mm located on the left somatomotor cortex (Paxinos and Watson, 1982). This injection causes generalized epileptiform activity characterized by large amplitude, spike, spike-wave and burst-like discharges in the recorded EEG or ECoG (Bagirici et al., 1999, 2001).

Data analysis

All ECoG data were continuously recorded on a personal computer's hard drive through a data-acquisition software (Chart 4.0.1, AD Instruments) and subsequent analysis of the ECoG data were performed offline. Online calculation channel recordings (including the spike amplitude and frequency calculations) were also performed during the experiments to monitor the severity of the epileptiform waves. At the end of the experiments, the position of the cannula was visually confirmed by 2% methylene blue infusion through the i.c.v. cannula after the animals sacrificed by cervical dislocation under anesthesia.

Recorded ECoG data were visually assessed offline and divided into three distinct episodes for each subject for FFT analysis (Fig. 1A):

1. Basal brain activity under urethane anesthesia (Fig. 1B).
2. Latent (silent) period which immediately follows the i.c.v. penicillin-G injection (the period in which the large amplitude ECoG components were significantly reduced; Fig. 1C).
3. Episode of mature epileptiform spikes (generally begins 15—30 min after the penicillin-G injection; Fig. 1D and E).

At least four minutes of continuous and noise-free segments of each episode were sampled for FFT analysis. Each sample than divided into 10-s non-overlapping windows and mean FFT values of each window were transferred into a spreadsheet program (MS Excel 2002) for further analysis. FFT values were obtained using a built-in extension (Spectrum) of the data acutisiton software (Chart 4.0), with Hamming windowing algorithm to minimize the spectral

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