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Effect of p-CPA Pretreatment on EEG Power Spectra in Experimental Open Brain Injury in Rats

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ABSTRACT

Continuous four hours EEG (electroencephalogram) recordings and its power spectrum analysis using fast fourier transform (FFT) in urethane anesthetized male Charles Foster rats were performed in two groups: open brain injury and p-CPA (para-Chlorophenylalanine) pretreated before brain injury, respectively, and compared with the EEG power spectrum of control rats. The EEG power spectrum analysis showed that there was a faster recovery in p-CPA pretreated group than the injury group of rats. The results showed that the p-CPA (a 5-HT inhibitor) prevents pathological changes following brain injury. Simultaneously, the inference can also be drawn that EEG power spectrum analysis is a useful technique for monitoring the brain injury and its recovery following pharmacological treatments. *Iran. Biomed. J. 7 (3): 119-126, 2003*

Keywords: Brain injury, p-CPA, EEG power spectrum

INTRODUCTION

Brain edema is considered as a untoward sequelae following traumatic, infective or metabolic insult to the central nervous system (CNS) [1] and if untreated, a progressive brain edema will lead to the compression of cerebral compartment resulting in an increased intracranial pressure and brain tissue softening. Excessive swelling of the brain in a closed cranial compartment will result in the depression of vital centers leading to death [2]. Therefore, in order to develop suitable therapeutic measures for such a common serious complication of brain disease occurring under a wide variety of noxious insults to the CNS, detailed study of progression, persistence and resolution of brain edema is very important.

Brain injury results in vasogenic edema due to the injury in the vascular elements and characterized by breakdown of blood-brain barrier (BBB) [3] that can be considered as one of the main factor contributing to morbidity and mortality of patients following brain trauma [4]. Various investigations have tried to explain the edema development following trauma in terms of specific alteration in the metabolism of particular neurotransmitters. It is suggested that 5-HT (5-Hydroxytryptamine), noradrenaline, adrenaline, dopamine, prostaglandins, histamine and glycine all play major role in the edema development following brain trauma [1]. Based on data obtained from different laboratories, a working hypothesis proposed according to which the widespread changes observed in focally traumatized brain has been mediated through a neurotransmitter system(s). According to the scheme of postulated inter-relationships between the release of substances by the lesion and alteration of synaptic function, it has been envisaged that prostaglandins and/or serotonin and/or catecholamines derived from injured brain tissue, induce changes in ionic channels in membranes causing functional depression [3].

Hypothalamic 5-HT is believed to be an important factor in regulation of ion distribution. The dorsal raphe nucleus contains the highest density of the serotonergic neurons and extends 5-HT fibers to the LHA (lateral hypothalamic area) [5]. High concentrations of immunoreactivity of serotonin positive fibers and varicosities from the dorsal raphe nucleus were found in some areas of the

*Corresponding Author; Tel. (91-6542) 27 9622; E-Mail: rksinha_res@rediffmail.com; **Abbreviations**: BBB, Blood-brain barrier; CNS, Central Nervous System; DFT, Discrete Fourier transform; EEG, Electroencephalogram; FFT, Fast Fourier transforms; 5-HT, 5-Hydroxytryptamine; Hz, Hertz (cycles/second); LHA, Lateral Hypothalamic Area; p-CPA, para-Chlorophenylalanine.

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hypothalamus including LHA axons ascending through the medial forebrain bundle [6]. Further, biochemical studies have shown that traumatic conditions cause a significant increase in the serotonergic activity in the brain and the destruction of the serotinin fiber system led to extravasations of fluid in the brain [2, 7-10]. Also, it has been suggested that in general, the drugs that are able to diminish 5-HT level in brain, thwart the edema development. In some series of experiment, it has been observed that edema development following stab injury have been remarkably reduced by prior administration of para-chlorophenylalanine (p-CPA), a 5-HT synthesis inhibitor that prevents edema development in experimental brain injury in rats [1, 10].

Monitoring and analyzing the electro-encephalograms (EEG) has been used in a variety of clinical situations including minor head injury [11, 12], acute hyperventilation [13], cerebrovascular surgery [14] and as a measure of anesthetic depth [15]. Among several signal-processing techniques applied for the EEG analysis, power spectrum using fast fourier transform (FFT) is the most popular approach to estimate frequency and amplitude changes [16] in different pathological and psychological states. The power spectrum analysis of EEG signals has been shown to be adequate in most quantitative procedures [17] as it conveys more information that usually not present in conventional analog EEG records [12, 18]. Previous laboratory experiments show increased amount of higher frequency immediately after head injury [19] and it's persistence for nearly two hours with significant reduction in power. In another experiment, p-CPA pretreatment was found prevented the flattening of EEG activity induced by acute immobilization stress [20]. Studies show that 5-HT plays a critical role in producing brain edema following brain injury that changes the EEG power spectrum. However, in p-CPA pretreated subjects followed by experimental brain injury, a long-term EEG power spectrum analysis has not been studied in a systematic manner so far.

In the present study, by considering EEG as a diagnostic tool, it has been tried to monitor that whether p-CPA pretreatment helps in stabilizing the EEG following brain injury or not.

MATERIALS AND METHODS

Subjects. All experiments were carried out on male Charles Foster rats (above six months old, weighing 200-250 grams) obtained from Central Animal House, Institute of Medical Science, Banaras Hindu University, Varanasi (India). The rats were individually housed in polypropylene cages (30 cm × 20 cm × 15 cm) with drinking water and commercial laboratory food pellets (Hindustan Liver Limited, India) ad lib. Ambient room temperature was maintained at 24 ± 1°C. The experiments were performed under urethane (Sigma Chemical Co., USA) anesthesia (1.8 gm/kg i.p.). The rats were divided into three groups: Control group (n = 10): Anesthetized rats with about 12 mm^2 of parietal cortex of right hemisphere exposed without trauma. Injured group (n = 10): Anesthetized rats in which about 12 mm^2 of parietal cortex of right hemisphere was exposed and injured (3 mm × 3 mm) using a sharp scalpel.

p-CPA pretreated group (n = 10). p-CPA (Sigma Chemical Co., USA) was injected i.p. (100 mg/kg) daily into the rats for three consecutive days [10]. Twenty four hours after the last injection of p-CPA, the animals were anesthetized. About 12 mm^2 of parietal cortex of the right hemisphere was carefully exposed and a stab injury like in injury group was made. The dose schedule inhibits the 5-HT synthesis in brain and induces a long lasting depletion in CNS [10].

Surgery and electrode implantation. Detailed method of electrode implantation was described by Sarbadhikari *et al.* [18] in brief, three stainless steel screw electrodes were aseptically implanted on the skull of the anesthetized rats. The coordinates for the parietal cortex were 2.0 mm lateral to the mid line and 1.0 mm anterior to lambda for one electrode and 1.0 mm posterior to bregma in right parietal region for another electrode. The reference electrode was placed at anterior most region of the skull. All animals were allowed a post surgery stabilization period of one hour before the onset of first recording. Injury was done between the recording electrodes after the stabilization.

Equipment. Cortical EEG had been recorded through a 8-channel electroencephalograph (Medicare, India). The electroencephalograph was also connected through a 12-bit ADC (Analog to Digital Converter) (ADLiNK, 8112HG, NuDAQ, Taiwan) with its supporting software (VISUAL LAB-M, Version 2.0c, Blue Pearl laboratory, USA) to record digitized EEG signals. For all recordings, processing and analysis purpose, IBM-PC (Pentium-III, 700 MHz) under WINDOWS-95 environment was used.

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Data collection and preprocessing. A single-channel bipolar EEG was recorded continuously from injury period to the first 4 hour of recovery. Recording was done with the sensitivity of 10 μV/mm. The analog cutoff frequencies were set at 0.3 and 70 Hz for high and low pass filters, respectively. Power line (50 Hz.) notch filter was used for entire recording for the rejection of AC line frequency. A sampling frequency of 256 Hz was used to acquire all components of EEG signals in digital form and to avoid aliasing. The digital data were stored on the computer hard disk in 2-minute data files at regular intervals. The time points have been used as discussed by Goel *et al.* [12] with slight modification of base line (the control period before subjecting the rats to any injury), just after the injury, 5, 10, 15, 30, 60, 120, 180 and 240 minutes after injury.

Data from each episode were fragmented in two-second epochs. Ten epochs from each episode were considered for spectral analysis. Each epoch was preprocessed for noise reduction before final power spectrum analysis. At first, the DC value was subtracted from the data and then the base line movement was reduced. In the final step of preprocessing, the data were band pass filtered with cutoff frequencies of 0.25 and 30 Hz, as the maximum frequency component of interest in anesthetized animal is less than 25 Hz [12]. The entire frequency spectrum of the filtered and processed data were subdivided in three bands to analyze three dominant frequencies (Fig. 1) that fall in the range of 1.0-5.5 Hz for low frequency, 9.0-14.0 Hz for medium frequency and 18-21 Hz for high frequency [12].

Spectral Analysis. The final processing of the EEG signals for the analysis of dominant frequency was performed by using power spectrum, which was developed to calculate discrete fourier transform (DFT) efficiently and rapidly. Recorded EEG responses consisting of short realizations of voltage against time were converted to the frequency domain by determining the discrete values of voltage at regular sampling intervals [21]. Using the DFT that transforms N discrete values to N discrete complex DFT amplitude and phase values carried out the conversion. Multiplication of the DFT components by T_s/N (where T_s is sampling interval) converts them to fourier transform components, the amplitude of which has dimensions of volts per hertz. A plot of the square of these amplitudes against frequency is referred as 'power spectrum'. For the present work, the power spectrum analysis was performed using 'Rectangular Window'.

Changes in BBB permeability. Evans blue dye (2% in 0.9% saline, 0.3 ml/100 g body weight) was injected through femoral vein before rats were sacrificed and dye extravasations on the brain parenchyma was noted through naked eye [2, 9].

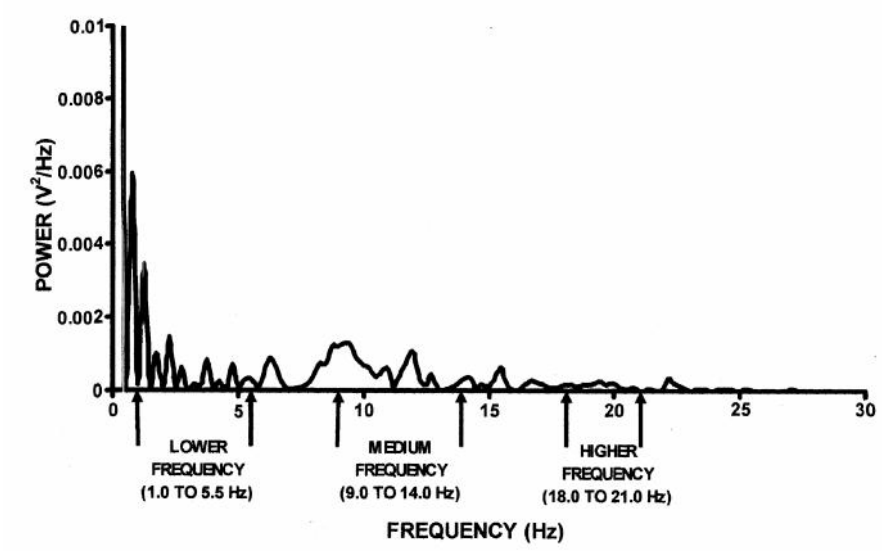


Fig. 1. A typical power spectrum of a two-seconds epoch of EEG signal and classification of EEG frequencies in three bands. EEG frequencies were classified as low frequency (-1.0 to 5.5 Hz), medium frequency (-9.0 to 14.0 Hz) and high frequency (-18.0 to 21 Hz).

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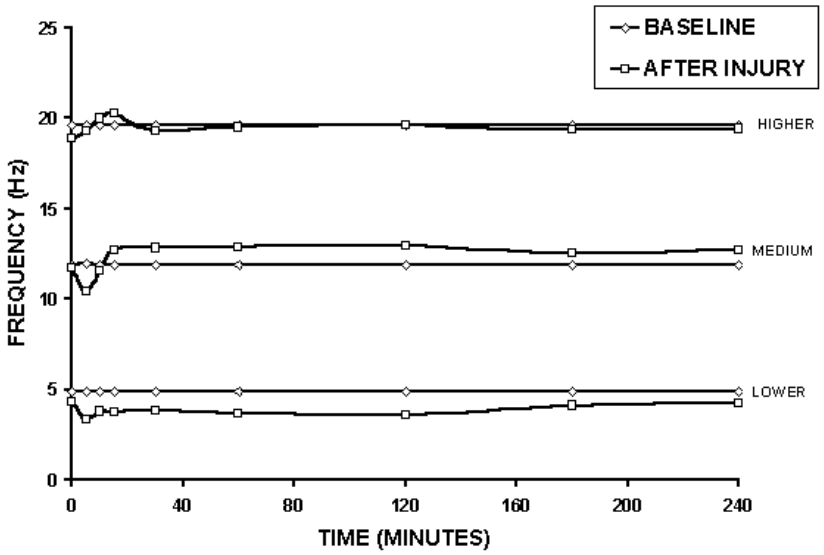


Fig. 2. Comparison of three dominant frequencies of EEG power spectrum in injury group of rats with the baseline frequencies at predefined time intervals.

Percent water content determination (edema and edematous swelling). Rats were sacrificed after 5 hours of surgery, and then the brains were taken out. The wet and dry weights of the brains were noted and water percentage for each brain was calculated. Dry weights of each brain were determined after repeatedly drying the sample in oven at 80ºC until the weight remains constant.

The percentage of edematous swelling was calculated using following formula [22]:

$$\frac{\%\ \text{Water content in control} + f}{100 + f} = \frac{\%\ \text{Water content in experimental animal}}{100}$$

Where f = % of swelling caused by edema.

One-way analysis of variance (ANOVA) was used to compare all the values of EEG frequencies and percentage of water accumulation.

RESULTS

Baseline EEG. The baseline EEG was recorded from control and injury group of rats (just before the injury). The low frequency components had the greatest power. The maximum average power of power spectrum of the baseline EEG was treated as normalized power and this power spectrum had treated as normalized power spectrum. The changes in all three mentioned frequency bands and relative powers of power spectrum of EEG at different intervals were compared from the normalized power spectrum.

EEG of injury group. Just after the baseline EEG recordings, rats were subjected to injury by the experimental procedure described in the methods. After injury, continuous EEG recordings were done for four hours and spectral analysis was performed on all nine times points, as mentioned earlier in the methods. The analysis of changes in frequency components, and relative power spectrum are presented in Figures 2 and 4, respectively. Significant changes were analyzed in lower (P<0.05) and medium bands (P<0.05) of EEG frequencies following the brain injury, which did not return to the control value in four hours of post injury EEG recording.

EEG of drug treated group. The spectral analysis for p-CPA pretreated group of rats was performed similar to the injury group of rats. The EEG power spectrum was also analyzed on all nine time points (Figs. 3 and 4). Statistical analysis result shows significant changes in all three bands of EEG frequency band (P<0.05) up to 30 minutes of injury. However, following one hour of brain injury, insignificant changes were analyzed in all three EEG frequency bands in p-CPA pretreated rats and this group of subjects showed faster and smooth recovery in EEG signals.

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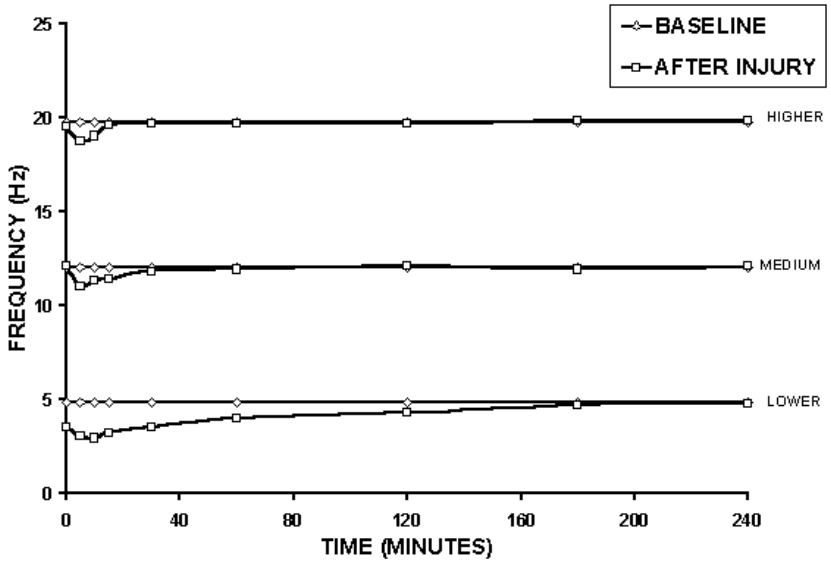


Fig. 3. Comparison of three dominant frequencies of EEG power spectrum in p-CPA pretreated group of rats with the baseline frequencies at predefined time intervals.

Changes in BBB permeability. A moderately-high concentration of Evans blue was seen at the vicinity of injury in the right half of the brain, whereas relatively less concentration was observed on the left half of the brain in drug untreated injured group of rats. However, a uniform distribution of Evans blue was seen on the both halves of the brain in p-CPA pretreated group of rats.

Percent water content determination (edema and edematous swelling). Injury group: Following the injury in cerebral cortex, the increase in water content was occurred in traumatized brain as compared to the brain of control rats (Table 1). The results show a highly significant rise in the percentage of brain water content (P<0.01) that

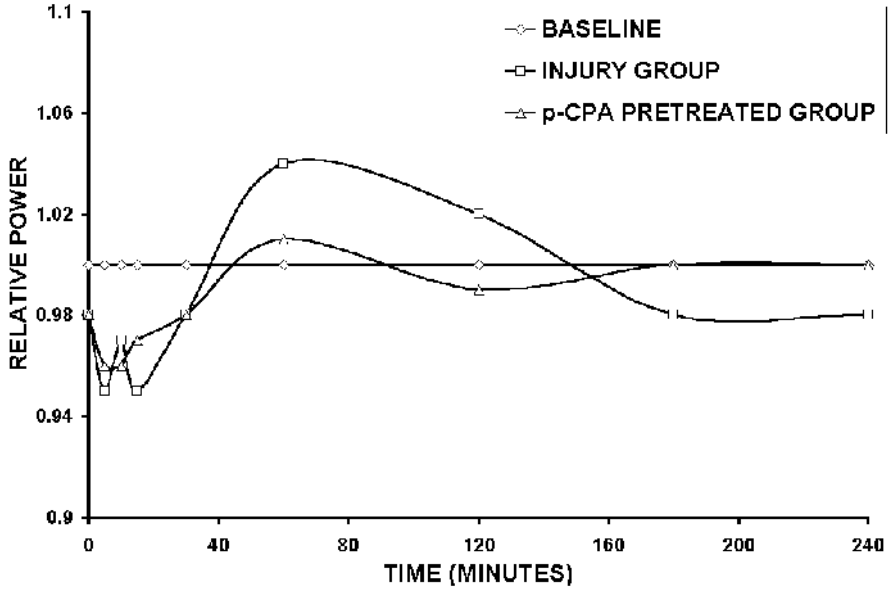


Fig. 4. Comparison of relative power of 'INJURY' and p-CPA pretreated rats with the baseline power at different time intervals.

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Table 1. The data of water content percentage obtained at the end of four hours from rat brains of control, injury and p-CPA pretreated groups.

Animal number	% Water content in the brain of 'Control' group of rats	% Water content in the brains	
		'Injury' group	'p-CPA pretreated' group
1	68.97	70.860	68.750
2	69.24	72.250	69.950
3	70.03	72.550	68.450
4	67.85	71.700	68.670
5	69.50	70.350	69.040
6	67.65	70.110	68.520
7	68.76	70.850	69.990
8	68.99	71.600	68.120
9	67.63	71.550	70.100
10	70.15	72.390	68.850
Mean ± S.E.	68.877 (0.27)	71.421 (0.25)*	69.044 (0.21)

Data are expressed as Mean (± S.E). The water content percentage in brain of 'injury' and 'p-CPA pretreated' groups of rats compared *$p<0.01$ to respective control rats. The difference of the mean value between 'injury' and 'control' groups was 2.54% that corresponds to 8.90% of edematous swelling in the brain of drug untreated 'injury' group of rats.

reflects severe edematous swelling in the brain of this group. The percentage of water accumulation in this group shows a significantly high rise (2.54%) with respect to control rats, which represents 8.90% of edematous swelling.

p-CPA pretreated group: Animals pretreated with p-CPA (5-HT inhibitor) show remarkable reduction of both the percentage of water accumulation as well as edematous swelling in the injured brain as compared to the drug untreated injured animals (Table 1). Data compared with the control rats show insignificant change in water content percentage in p-CPA pretreated group.

DISCUSSION

EEG has been considered as one of the potential candidates to monitor brain injury and the effect of drugs on CNS [23] but inter-observer variability in its analysis has limited the use of this task. In the present study, we have tried to monitor and analyze EEG variations following experimental brain trauma and the effects of brain injury on brain electrical activities using EEG power spectra. The EEG power spectrum interpretations based on dominant frequency analysis is effectively reducing the experimental data, while preserving important features such as time varying changes, dominant frequency components, their amplitude and power [12]. For the better peak resolution, the power spectrum was smoothed using method described earlier [24, 25]. During the baseline EEG recording, powers of three dominant frequency components were remained stable to their respective baseline values. Thus, it is assumed that EEG in anesthetized rats shows low variations.

Data analyzed from the injury group of rats revealed that among three dominant bands of EEG frequencies, low (0 to 5.5 Hz) and medium (9 to 14 Hz) bands showed significant changes following brain trauma. However, higher band show insignificant variations after initial drift following brain injury. The frequency components of medium band showed biphasic patterns. It was found depressed in the initial period of EEG recording following brain injury while the lower frequency components were observed depressed in four hours of post injury recordings. The comparative spectral analysis of EEG signals from the injury and p-CPA pretreated rats indicate that the frequency and power of EEG signals in the injury group were not recovered during four hours of recording. The components of lower frequency band were tending to recover but the recovery was very slow, whereas the medium frequency band was seen disturbed and there were no indications of recovery. All the three frequency bands show same phenomena in initial recordings, namely the dispersion in dominant frequency components due to the insult. This dispersion may be due to a shift to a lower sleep stage in response to traumatic challenge [12].

Alternatively, it may result from altered electrical activity of neurons and neural networks in brain cerebral cortex. On the other hand, in p-CPA pretreated rats, EEG frequencies and power were seemed to be faster with smooth recovery in four hours and the EEG signals were found to be recovered fully. After one hour of recovery from the injury, lower frequency components of p-CPA pretreated group were observed to approaching the baseline values. At the same time, the bands of the

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medium and high frequency did not show any major changes in the drug-pretreated rats in comparison to the control values. Thus, in p-CPA pretreated rats, the changes in EEG signals following brain injury was reversed due to the inhibition of 5-HT secretion.

In CNS, 5-HT is believed not only as a neurotransmitter but also as a cause of injury in some pathological processes as it accumulates at the injury site. So, in craniovascular walls, brain and spinal cord following traumatic insult, increased concentration of 5-HT was observed [9, 26]. The release of 5-HT following brain trauma may influence the synaptic activity and increase the blood-brain permeability [10, 27]. It has already been established that under light urethane anesthesia, animals exhibited patterns of cortical activities similar to those seen in wake; drowsiness and slow wave sleep as in unanesthetized animals [28, 29]. On the other hand, the involvement of 5-HT in inducing synchronized sleep in mammals is also well established [30]. Therefore, the increased 5-HT level following open brain injury may be responsible for the synchronization of EEG frequencies that enhance the medium band frequency components in EEG power spectrum.

The edema formation following the injury in rats, pretreated with p-CPA, was found abolished in 4-5 hours due to its inhibitory action in accumulation of 5-HT in experimental brain trauma. Sharma *et al.* [10] have extensively studied the effect of p-CPA pretreatment in CNS and reported that p-CPA has prevented the edema development in all groups of brain and spinal cord injuries irrespective to anesthesia, mode of injury or hypothermic state of animals [1, 10]. The only report on the study of p-CPA pretreatment on electrophysiology of rats was performed on the spinal cord evoked potentials [10, 27]. They reported that p-CPA pretreatment prevents the initial decrease in maximal negative peak amplitude of spinal cord evoked potentials and also the increase in water content. Earlier report on the study of EEG signals under acute immobilization stress also suggested that p-CPA pretreatment prevent flattening of EEG signals.

Studies of craniocerebral injury and the effect of p-CPA pretreatment in the brain trauma in anaesthetized rats have probably not been done previously by considering EEG as a diagnostic tool. With the support of the study of brain edema formation and the extravasations in BBB, the inference can be drawn that in p-CPA pretreated animals, the formation and accumulation of 5-HT was suppressed. Hence, the fluid accumulation at the injury site and the extravasations of the fluid due to BBB opening were also diminished. So, the recovery of the brain injury was observed faster as shown by the EEG spectral analysis. Results were compatible to the earlier report of Sharma *et al.* [10] on traumatic spinal cord edema and the effect of p-CPA pretreatment in evoked potentials.

The present study found that the three dominant frequencies provide a pretty robust estimate for most of the EEG similarly as reported by Goel *et al.* [12]. The present analysis was based on one channel EEG data. However, better diagnosis can be obtained by more effective monitoring of multi-channel data recorded for longer periods. Aside that, the EEG spectrum analysis shows clearly and accurately that p-CPA is responsible for faster recovery in brain traumatic insults. Thus EEG signal analysis can be used as an effective diagnostic tool for observation and monitoring of brain traumatic injury and its electrophysiological conditions following drug treatment. Further, the correlation of brain serotonin level with EEG signals in experimental brain injury cases in anesthetized rats are not well known and hence need detailed study.

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