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Spectral and Fractal Analysis of ECoG in Animal Model of Aluminium Intoxication

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Abstract: This paper presents an overview of rat animal model of Alzheimer's disease. Model is based on the toxicity, oxidative stress and neurodegeneration. The model is obtained by treatment of rats with intraperitoneal aluminum. Electrocortical group neuron activity describes changes in neurotransmission caused by different factors. Such changes could be qualitatively described by spectral and fractal analysis of electrocortical activity as a variation of the relative spectral power. Both animals and patients with Alzheimers demention have increased relative spectral power in delta range. By fractal analysis we described changes in electrocortical activity of aluminum intoxication animals compare to physiological control. We used change in delta range to calculate fractal dimension. Also we used fractal dimension to compare treated animals with control ones to quantitatively describe the degree of pathophysiological state. All changes are correlated with an increase in the relative spectral power in the delta range and can be quantitatively described by fractal dimension. Results are presented as the effect and can also be applied to the human model of neurotoxicity and neurodegeneration like Alzheimer's dementia. The model itself may be used for diagnostic and prognostic purposes since it describes the parameters underlying Alzheimer's disease. However in definition of disease should be consider a state of dementia and menthal activity.

Keywords: Toxicity; Ionian disbalans; Oxidative stress; Fractal analysis; Spectral power.

1. Introduction

Aluminum is known as a neurotoxic element widely distributed in nature. Epidemiological studies have shown that aluminum is one of the risk factors for the occurrence of Alzheimer's disease. Toxic effects of aluminum in rats are manifested as an increase in the relative spectral power in the delta range [1, 2].

All changes in the delta range of neuronal activity are in accordance with the same pattern of Alzheimer's disease. Neurological manifestations of aluminium intoxication are associated with oxidative stress and blood-brain barrier impairment [3]. The correlation with disease is the direct consequence of the disruption of ion homeostasis in the brain, and the symptoms are correlated with activation of compensatory mechanisms at the molecular level and neurophysiological activity [4]. ECoG describes changes related to the onset of disease (cytotoxicity, ionic imbalance and accumulation of aluminum), as well as secondary changes: oxidative stress, and alterations in the activity of neurotransmitters such as acetylcholine and glutamate.

The subject of this study was to describe changes in neuronal activity that are correlated with the onset of Alzheimer's disease in rat animal model of aluminum intoxication.

2. Materials and Methods

All animal procedures were complied with the European Communities Council Directive (86/609/EEC) and were approved by the Ethical Committee for the Use of Laboratory Animals of the Institute for Biological Research, University of Belgrade. We used 2-2.5 months old male Wistar rats reared under standard laboratory conditions (23±2 °C; 60-70% relative humidity, 12 h/12 h light/dark cycle with lights on at 07:00 h, unlimited access to food and water). The rats were intraperitoneally treated with a solution of aluminum chloride hexahydrate at a dose of 2-6

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mg/kg per day. Treatment lasted for 4 weeks. ECoG registration was done under anesthesia (Nembutal or Zoletil) and we registered the activity of parietal cortex and cerebellar cortex. Analog to digital conversion was performed with a sampling frequency of 256 Hz. Spectral analysis of ECoG activity was performed by Fourier transformation for signals lasted 120 s (divided into 15 epochs lasting 8 s). Fractal dimension was calculated by Higuchi algorithm [5].

3. Results

Alteration of the relative spectral power in the delta range in terms of its increase is a direct consequence of changes in neural transmission and functional relationships. Figure 1 shows the average increase in the relative spectral power in the delta range, which can be considered as an indicator of risk for the onset of Alzheimer's disease. Standard deviation describes changes in ECoG activities which are not correlated with the onset of disease and are physiologically normal. Changes in the theta activity in animal model are different from those in Alzheimer's disease and standard deviation describes differences between the model and the condition of disease. The delta/theta ratio indicates the effects of toxicity. Linearization indicates that all changes below the line are in the normal range, while changes above the threshold of tolerance are in case of larger variation of the delta and theta.

In Figure 1 is presented a typical case of changes in neuronal activity and ion homeostasis, as well as secondary changes in neurotransmission which are a consequence of the disruption of the brain function integrity. This situation is analogous to the state of disturbed homeostasis which can lead to disease.

Figure-1. The relative spectral power in A1 rat

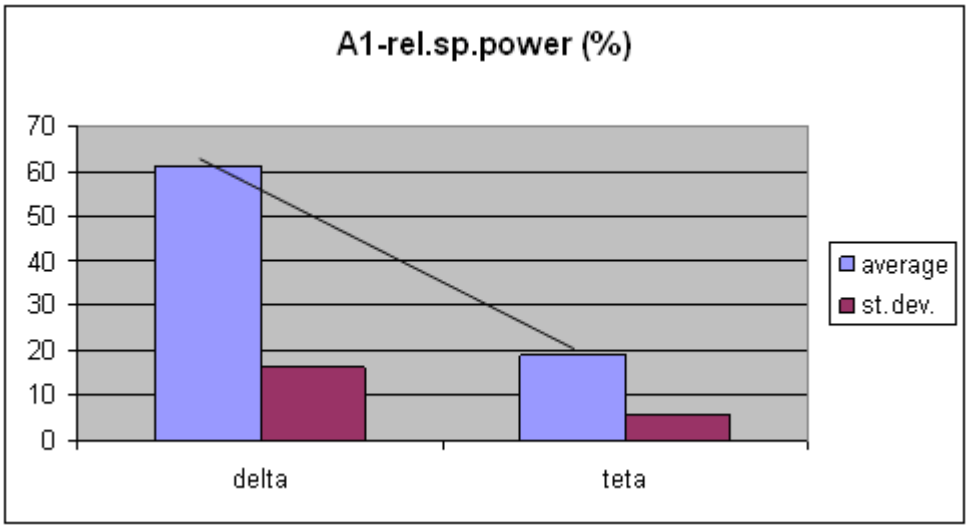
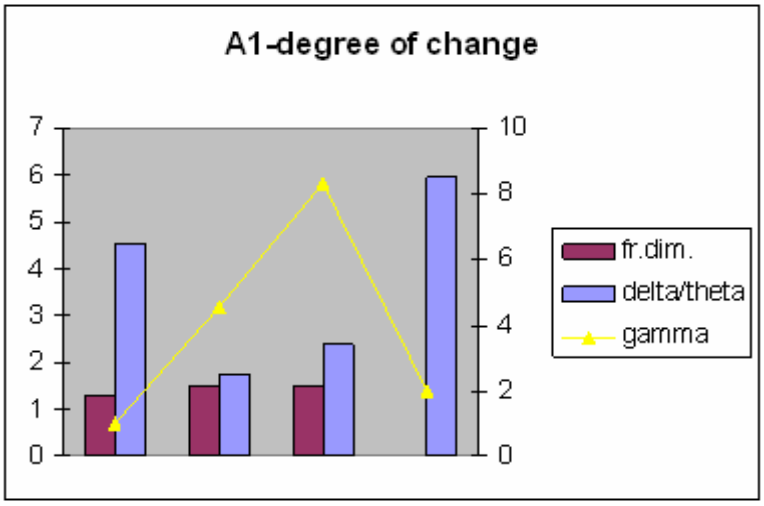


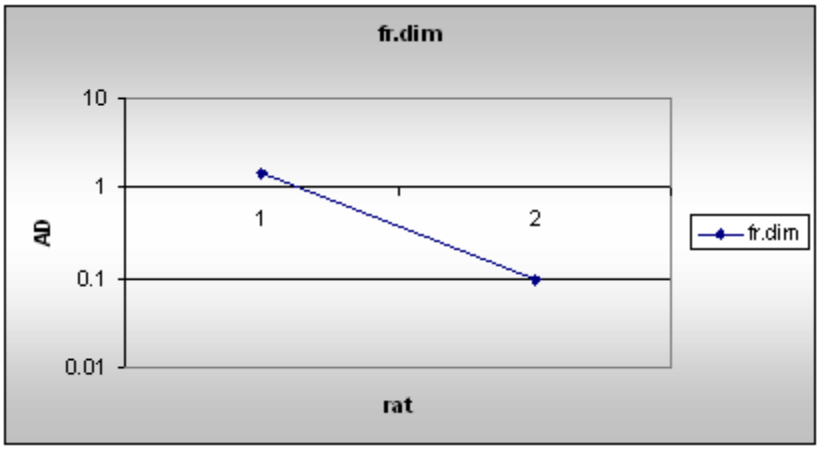
Figure 2 presents alterations of the delta / theta rhythm which indicate the size of changes due to toxicity, and fractal dimension of ECoG activity which indicates the physiological integrity of the brain function. Changes in the gamma activity indicate secondary damages and reparative mechanisms. Linearization suggests that changes above the line in terms of increasing delta rhythm and decreasing theta rhythm can be characterized as pathophysiological condition. In this case, fractal dimension fluctuates due to compensation between the slow wave range and higher frequency ranges. The increase in delta/theta ratio and decrease in the gamma activity indicate unphysiological changes and is presented in Figure as the right column.

Figure-2. Change in the relative spectral power and fractal dimension – size change



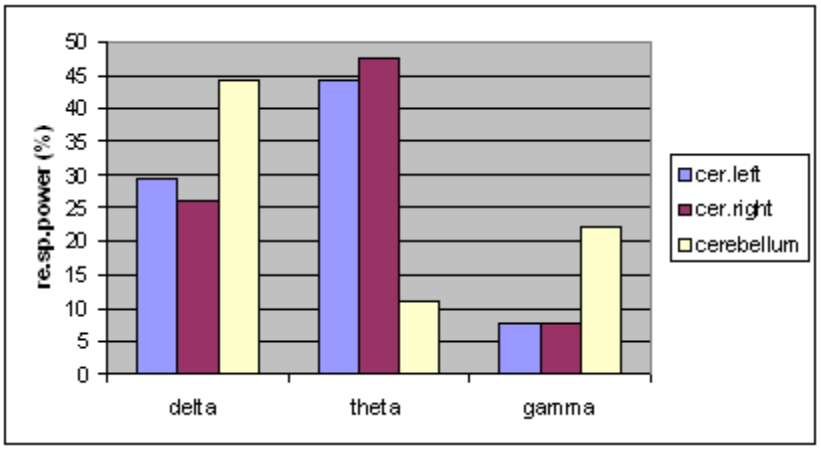
In Figure 3 is presented fractal dimension of ECoG in A1 rat in the group of the same animals treated with aluminium at a dose of 2 mg/kg per day. This model includes fractal dimension fluctuations depending on the pathophysiological condition. Fractal dimension of 1.4242 represents the mean value which corresponds to a change of 0.1-1%. It can be seen that the higher values of fractal dimension mean less change while reducing the values of fractal dimension can be an indicator of the onset of disease, as well as a parameter in the prognosis of disease.

Figure-3. Fractal dimension and its change in animal model of Alzheimer´s disease



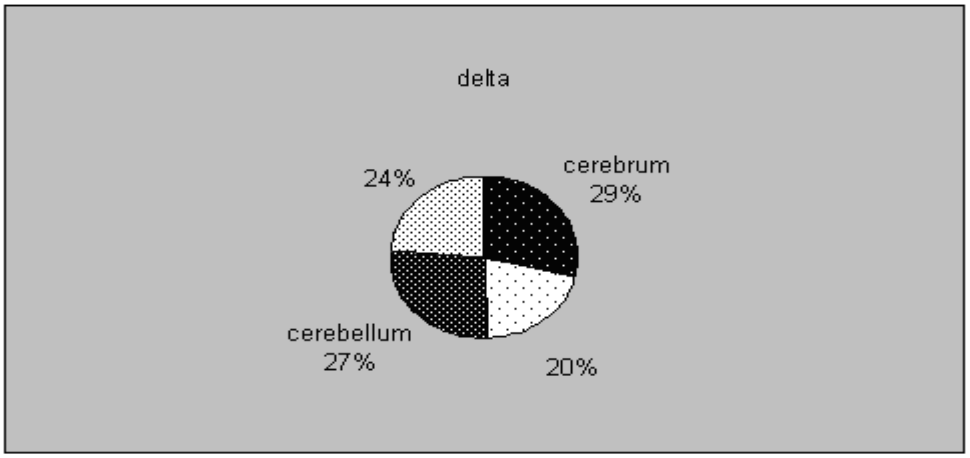
In Figure 4 is presented the activity of the cerebral cortex and cerebellar cortex in conditions of oxidative stress (rat treated with aluminium at a dose of 4-6 mg/kg). It can be seen that the change of rhythm is in relation to the activity in the theta range, as well as that the answer is different in the cerebrum and cerebellum. At the level of the cerebrum, the increase in theta activity is a result of activity in conditions of oxidative stress. At the level of the cerebellum, the delta and theta activities are desynchronized.

Figure-4. The relative spectral power in the cerebrum and cerebellum in conditions of oxidative stress



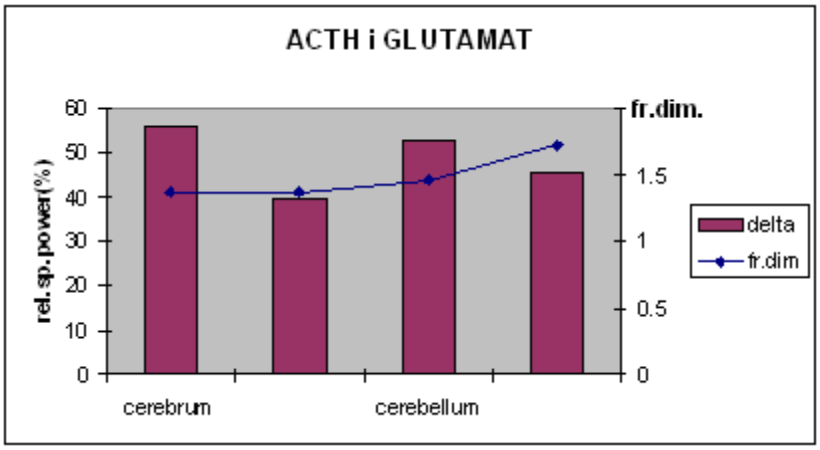
In Figure 5 is presented alteration of the delta rhythm in non-stress conditions and neurodegeneration (young rat treated with aluminum at a dose of 2 mg/kg). It can be seen a slight increase in the relative spectral power due to changes in synaptic transmission. This change is relative and is not adaptable, but fluctuates.

Figure-5. The delta rhythm in conditions of altered synaptic transmission



In Figure 6 is presented change in acetylcholine and glutamate, which is a result of cytotoxicity and is increased in Alzheimer´s disease. As it can be seen, it is different in the cerebrum and cerebellum. The increase in fractal dimension in the cerebellum may be an indicator of neurotransmission changes.

Figure-6. Neurotransmitter changes in conditions of cytotoxicity



4. Discussion

Neurological manifestations of aluminium intoxication are associated with stress, oxidative changes, disruption of ion homeostasis and the blood-brain barrier. It has been shown that intoxication and accumulation of aluminum in the brain have cumulative effect which is determined by tissue selectivity, connections in the brain and dose of aluminium. The correlation with disease is the direct consequence of the disruption of ion homeostasis in the brain, and symptomatology of disease is a secondary effect of activation of compensatory mechanisms for damage at the molecular and neurophysiological levels. In the model of aluminium neurotoxicity, as an indicator of changes, it was analyzed the delta rhythm which is correlated with all the aforementioned changes. It was achieved by fluctuation of anesthetic dose and by maintaining a state of pain suppression. In this model, the alpha range is related to cognitive and intellectual capabilities, while the beta range is related to motor performances. The gamma rhythm is observed in accordance with the previously developed model of tissue lesions during registration. Increase in the delta rhythm may be due to several factors, of which we observed stress, disruption of the blood-brain barrier, neurotransmitter modulation, inflammation and neurodegeneration.

Regarding neurotransmitters, intoxication is most pronounced in glutamatergic transmission, but in animal model of electrocortical registration under anesthesia it is maximally potentiated by the effect of anesthetic on GABA inhibition.

The use of different anesthetics (Zoletil, Nembutal) indicates fluctuations in glutamatergic transmission. Also, teratogenic effect is a consequence of excessive excitation of neurons by glutamate in conditions of reduced metabolic production of GABA. The accumulation of aluminum in the brain tissue leads to the disruption of Ca homeostasis. The response is production of glutamate in high concentrations which affects postsynaptic neurons. In the model of chronic glutamatergic intoxication it can have a global effect on the brain level [6]. Increased glutamatergic transmission is implicated in cell death and degeneration. These effects are present in disorders such as olivopontocerebellar atrophy, Huntington's disease, epilepsy, hypoxia, ischemia and hypoglycemia [7].

Oxidative stress is a consequence of increased peroxidase activity, oxidation-reduction reactions, accumulation of free radicals, mitochondrial aberration, and decreased ATP production. Aluminum toxicity and neurodegenerative processes have been studied in correlation with Alzheimer's disease [8]. Neurodegenerative processes are present in older animals. Activation of apoptosis is accompanied by degeneration. It is assumed that gene mutations alter the structure of toxic cell. Neurodegeneration leads to conduction loss and gliosis, and rarely inflammation.

Electrophysiological, behavioral and histological analyses showed that neurotoxicity is a consequences of oxidative stress, which damages membrane lipids, the activity of membrane proteins (Na-K-ATPase and PKC) and antioxidant enzyme activities (SOD, GPx and GST) [9]. Aluminium causes oxidative stress by neurochemical changes. The first change is reduction of vesicular transport, and consequently reduction of microtubule-based transport, ATP in axonal mitochondria, and synaptic vesicles, as well as changes in Golgi complex. Oxidative changes are production of malondialdehyde, carbonyls, peroxynitrite, nitrotyrosine, SOD, and heme oxygenase [10] . Apoptosis occurs due to accumulation of aluminum in the cells, which leads to depolarization and inhibition of Na-Ca pump, and consequently accumulation of Ca^{2+} in mitochondria and endoplasmic reticulum. Apoptosis is a genetically determined and activation of caspase proteases induces genetic change [8].

5. Conclusion

It can be considered that the relative increase in spectral power in the delta range acts as an indicator of change in physiological state in conditions of disturbed homeostasis in Alzheimer's disease. Molecular, biological and physiological changes underlying disease have been described as oxidative stress, changes in neurotransmitter

activity, inflammation and neurodegeneration. These changes are manifested to a different extent through the increase in the delta rhythm. In this animal model, changes in the higher frequency ranges are not comparable with Alzheimer's disease and require to be analyzed differently. The increase in the delta activity has diagnostic and prognostic significance.

Acknowledgements

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