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SPONTANEOUS CEREBELLAR ACTIVITY AND ITS ROLE IN NEUROTOXICITY

SPONTANA AKTIVNOST MALOG MOZGA I NJEGOVA ULOGA U NEUROTOKSIČNOSTI

Ljiljana MARTAĆ, Gordana STOJADINOVIĆ and Branka PETKOVIĆ

Summary
Introduction. In performed experiments, the parietal electrocortical activity of the cerebral cortex and the activity of the cerebellar cortex were simultaneously recorded. The main purpose was to compare their spontaneous activity, as the recording was conducted during anesthesia. **Material and Methods.** We used 2–3 months old rats weighing 200 – 350 g. Two groups of rats with same characteristics were made. The first group of 15 rats (control group) was recorded under anesthesia and there was a change in spectral power in accordance with frequency ranges. The second group of 30 rats was recorded under the same experimental conditions, but the rats were treated intraperitoneally by aluminium chloride hexahydrate solution or with 1.5% solution of aluminium chloride hexahydrate per os. **Discussion.** Changes in spontaneous activity of the cerebellum during aluminium intoxication were compared with control values. It was shown that lesion and neurotoxicity during stable anesthesia led to desynchronization of the cerebellar activity. This is described by the change in fractal dimension of cerebellar electrocortical activity. The assumption is that the inhibition caused by anesthetic is compensated during aluminium intoxication. **Conclusion**. The cerebellum plays a role in compensation through changes in spontaneous activity. This response involves an increase in the value of fractal dimension of cerebellar electrocortical activity which is reduced in neurotoxicity.
Key words: Aluminum; Cerebellum; Action Potentials; Neurotoxicity Syndromes; Neuronal Plasticity; Adaptation, Psychological; Rats; Anesthesia

Sažetak
Uvod. U eksperimentima je uporedo registrovana elektrokortikalna aktivnost parijetalne kore velikog mozga, kao i aktivnost kore malog mozga. Cilj je da se uporedi njihova spontana aktivnost jer se registrovanje vrši u anesteziji. **Materijal i metode**. U istraživanju smo koristili pacove starosti 2 - 3 meseca, telesne mase 200 - 350 g. Formirane su dve grupe pacova sa istim karakteristikama. Kod prve grupe, koju cinilo je 15 pacova (kontrolna grupa) ispitivanje je rađeno u anesteziji, zabeležene su promene spektralne snage u skladu sa obimom frekvencije. Druga grupa od 30 pacova je ispitivana pod istim eksperimentalnim uslovima, ali su pacovi tretirani rastvorom aluminijum hlorid heksahidrata, ili 1.5 % rastvorom aluminijum hlorid heksahidrata *per os*.**Diskusija**. Promena spontane aktivnosti malog mozga u uslovima intoksikacije aluminijumom je poređena sa kontrolnim vrednostima. Pokazano je da lezija i neurotoksičnost u uslovima stabilne anestezije dovode do desinhronizacije aktivnosti malog mozga. Ovo je opisano promenom fraktalne dimenzije elektrokortikalne aktivnosti. Pretpostavka je da se inhibicija izazvana anestetikom kompenzuje u uslovima intoksikacije aluminijumom. **Zaključak**. Mali mozak ima ulogu u kompenzaciji putem promene spontane aktivnosti. Ovakav odgovor podrazumeva povećanje vrednosti fraktalne dimenzije elektrokortikalne aktivnosti malog mozga koja je u uslovima neurotoksičnosti smanjena.
Ključne reči: aluminijum; mali mozak; spontana aktivnost; neurotoksični sindromi; neuroplastičnost; adaptacija; pacovi; anestezija

Introduction

Cerebellar electrocorticographic (ECoG) activity is characterised by the presence of synchronized oscillations. Synchronization involves oscillation of two or more different structures that are at the same phase. There are two hypotheses on the role of synchronized oscillations: a role of testing conditions, or in the preparation of motor activities [1]. It is known that the cerebellum has other roles as well, such as: regulation of motor activities, cognitive processes, role in motor studying, and cognitive function.

A group activity of neurons of the cerebral and cerebellar cortex was recorded. The recording of the parietal cortex was carried out in order to monitor changes due to anesthesia. The electrocortical activity of the cerebellar cortex was recorded at different depths (0.5 - 1.5 mm) for the purpose of getting an insight based on local potentials of the cortex field, of the entire cortex activity in coordination with other cerebellar structures (cerebellar network).

Previous research of parietal cerebral cortex lesion revealed the specific role of the cerebellum in reparation of the damaged function - plasticity [2]. Also, the

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Abbreviations

ECoG – electrocorticography
FD – fractal dimension
DC – direct current
GABA-A – gamma-aminobutyric acid type A

tested activity was monitored in different experimental conditions and types of anesthesia [3] in order to cover all changes in the activity of various layers of the cerebellar local circuit. During stable anesthesia (the same relative spectral power of the cerebellum and delta activity of the cerebrum of approximately 45%) we recorded a spontaneous activity of rats' cerebellum under controlled conditions and after aluminium treatment. The neurotoxic effect of aluminium can be described by spectral and fractal analysis [4]. The oscillating cerebellar activity is associated with fluctuations between excitation and inhibition of the cerebellar structures [5].

Changes in spontaneous activity during anesthesia and aluminium intoxication led to desynchronization of the rhythm and change in the balanced state**.** During anesthesia, this change is offset by a change in neurotransmission, while in aluminium intoxication, this activity has been altered. Since anesthesia and aluminium intoxication have different mechanisms of action and affect the entire cerebellar network, it is possible to monitor the role of the cerebellum, that is, to monitor the adaptability and plasticity as a difference in the spontaneous activity in anesthetized and intoxicated units. It is possible also, by comparing their activity, to quantify the change by calculating values of the fractal dimension (FD) of electrocortical activity. The anesthetic effect is reversible, while in aluminium intoxication there is an adaptable response. An increase in FD of electrocortical activity during anesthesia suggests a change in the activity of cerebellum, which is related to neurons' inhibition and excitatory connections blockade. Variable values of FD electrocortical activity in aluminium intoxication indicate changes in neurotransmission which differ from mechanisms of anesthesia and are responsible for the change in the state of the cerebellar network. The difference in FD of electrocortical activity between these two conditions (intoxication and anesthesia) is in compliance with the adaptive ability of the cerebellum.

Material and Methods

In this experiment, male Wistar and Sprague Dawley rats were used. By using these different sorts of rats, it was possible to monitor stereotyped functions and individual variability that changes due to change in physiological parameters. The animals were kept in cages, with 12-hour exposure to light and 12-hour exposure to dark, with an unlimited access to briquetted food and water, at a temperature of 18 to 21°C. These uniform breeding conditions allowed us to compare different sorts of rats. All experiments were carried out in compliance with the Directive 2010/63/EU on the protection of animals used for experimental and other scientific purposes and was approved by the Ethics Committee of the Institute for Biological Research "Siniša Stanković", University of Belgrade.

We used 2–3 months old rats weighing 200 – 350 g. Two groups of rats with same characteristics were made. The first group of 15 rats (control group) was recorded under anesthesia and there was a change in spectral power in accordance with frequency ranges. The second group of 30 rats was recorded under the same experimental conditions, but the rats were treated intraperitoneally by aluminium chloride hexahydrate solution or with 1.5% solution of aluminium chloride hexahydrate per os. The procedure of aluminium intoxication lasted at least 4, and at most for 6 weeks, so the rats were just over 3 months old at the time of recording. The surgical procedure for setting-up the electrodes was carried out on animals anesthetized with nembutal (Pentobarbital Sodium, SERVA, Heidelberg, Germany) or by zoletil (Virbac S., A. Carros, France), which was given intraperitoneally (i. p.) at a dose of 45 mg/kg of nembutal i. e. 60 mg/kg of zoletil. Even though the molecular mechanisms of these two anesthetics are different, their effects are similar and involve an increase of the relative spectral power in the delta range. During the experiment, anesthesia was added at a dose of about 8 mg/kg. The anesthetized animals were fixed in a stereotaxic frame. Afterwards, a craniotomy was carried out, and electrodes were set up. Craniotomy was carried out on parietal bones, by drilling round holes 2 mm in diameter, with coordinates: 2 - 2,5 mm posterior to the bregma and 2 mm lateral to the sagittal suture, and 10,5 mm posterior to the bregma and 1 - 1,5 mm lateral to the sagittal suture [6]. The activities in the parietal and cerebellar cortex were recorded simultaneously. Changing the position and the insertion depth of electrodes showed that there was an overlap of the recorded local field potentials, describing the parietal activity during anesthesia, as well as in the entire cerebellum together with all cerebellar structures. Delta activity is predominant in anesthesia and its activity in the parietal cortex is variable in anesthesia. Signals recorded at 5 - 15 min were selected, after anesthesia and in stable anesthesia, and a value of about 45% of the relative spectral power of delta range of the cerebral cortex was selected. During stable anesthesia, changes in the delta and theta rhythm of the parietal cortex were monitored, showing the level of intoxication. During stable anesthesia, as well as during exposition to neurotoxicity, there was a selection of signals in the cerebellar cortex. We compared the activity in the cerebellar cortex during stable anesthesia with the changes of slow-wave components in intoxication. Recording of the activity in the cerebral parietal cortex and cerebellar cortex was performed by tungsten electrodes which were positioned at 0,5 - 1,5 mm within the cerebral cortex. The recordings were done at different depths, in order to describe the average activity of the local circuit of the cerebellum, including all the structures. By selecting a signal with a certain relative spectral power, we achieved uniformity, thus avoiding variability due to anesthesia and intoxication that vary due to various applications or doses of aluminium. Only neurotoxicity in experimental models was monitored by increasing the delta and theta rhythms, thus avoiding differences due to uneven application of aluminium, as well as dose dependency and length of the treatment. Signals were observed on an oscilloscope (Textronix, USA). Amplification of the signal was carried out using the Multi Channel Processor-Plus (Alpha Omega Engineering, Israel) amplifier. Filtering of the signals was performed as well. The filter parameters were direct current (DC) for high-pass filter and 150 Hz for low-pass filter. The entire experiment of recording the cerebral cortex was performed in 30 - 120 min. The recording of brain's activity was performed at intervals, every 5 – 10 min, and lasted for 121 sec. In this way, we have made a signal file recorded at every 5 min for 120 min with signals lasting 121 seconds, which is optimal time frequency of 128 Hz.

Analogue digital conversion was carried out at a sampling frequency of 256 Hz. Recording was performed with 4 i. e. 2 tungsten electrodes, with one electrode for grounding. All data were recorded with a program for signals' acquisition SIGVIEW [7].

The analysis of the recorded electrocortical activity in the cerebral and cerebellar cortex was carried out in FORTRAN programs under DOS operating system and in the Matlab 6.5. Program, Windows operating system. We used programs designed by the associates of our neurophysiological laboratory (Janković B, Kalauzi A). The recorded signals were filtered at 50, 60 and 101 Hz and any possible irregularities (drift, interferences and movements) were excluded from the analysis.

The recorded 121 seconds-long signals were saved as binary files. For each recorded signal, Fourier transformation was performed for 15 epochs that lasted 8 sec. The obtained power spectra (relative spectral power) were compared and the mean value of the entire recording experiment was calculated, and a standard deviation was determined. Within analysis of spectra, we monitored the relative spectra power at frequency ranges: delta (0,1 - 4 Hz), theta (4,1 - 8 Hz), alpha (8,1 - 15 Hz), beta (15,1 - 32 Hz) and gamma range (above 32 Hz).

Fractal analysis belongs to a group of nonlinear ECoG analysis methods. The value of FD of electrocortical activity was calculated using the Higuchi's algorithm [8, 9]. The size of non-overlapping window was 200 points, which corresponds to an epoch of 0,781 seconds at a 256-Hz sampling frequency. In regard to k_{max} parameters, an optimal value of k_{max}=8 was established [10]. Based on the obtained FD electrocortical activity of individual windows, the mean value and standard deviation of the FD electrocortical activity of the entire signal was estimated. The FD values of electrocortical activity range from 1,000 – 2,000.

The power spectrum was described by statistical parameters, i. e. mean value and standard deviation for 15 registered epochs. Also, the entire procedure of recording was done in each experimental animal, determining the mean value and standard deviation. This kind of descriptive analysis provides data on the distribution of relative spectral power across frequency ranges. The mean value indicates grouping of the variable value, while the standard deviation indicates its variations. In a group of similar population with a group of individuals with similar characteristics of the delta rhythm, the hypothesis tested changes in biological parameters by t-test with a level of significance of 0,05. These tests indicate changes in the activity of a group of neurons within the neurotransmitter size, or with respect to the connection between the cerebral regions and the change in functionality of this connection. This experiment includes both changes in the activity of the brain due to aluminium intoxication.

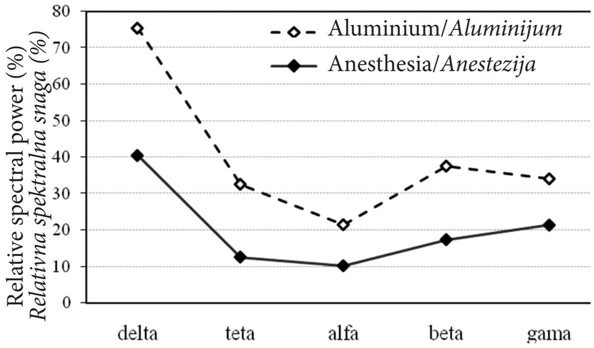
Results

Table 1 shows results obtained by comparing rats treated with aluminium (2 mg/kg i. p.) and rats exposed only to the effects of anesthesia, i. e. they were not treated with aluminium. Spectral analysis showed the change in the relative spectral power of the signal in different frequency ranges (delta, theta, alpha, beta and gamma range). Increase in the relative spectral power due to anesthesia effects (Zoletil) in a model of aluminium neurotoxicity in the delta range is an indicator of neurotoxicity and compared to the group of anesthetized rats (dominant delta range), it differs in the cerebrum and cerebellum. Namely, due to inhibition and lack of sensory-motor functions, we can talk about spontaneous activity of neurons of cerebral and cerebellar cortex in the anesthetic state, as well as change of the spontaneous activity due to neurotoxicity. Both anesthesia and neurotoxicity showed increased relative spectral power in the delta range, but mechanisms of action are different. By comparing activities during anesthesia and during intoxication, we obtained a full picture on spontaneous activity and its changes.

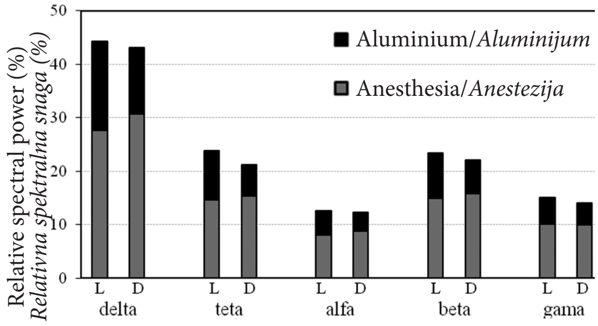
In the experiments, we have simultaneously recorded the parietal electrocortical activity of the cerebral cortex activity in order to monitor changes after anesthesia, based on the relative spectral power in the delta range, as well as different cortex layers of chemosphere of the back cerebellar lobe **(Table 1)**. The ob-

Table 1. Changes in the relative spectral power in frequency ranges of the cerebrum and cerebellum, anesthesia vs. treatment with aluminium (2 mg/kg i. p.)
Tabela 1. *Promena relativne spektralne snage po frekventnim područjima za veliki i mali mozak, anestezija vs. tretman aluminijumom (2 mg/kg i.p.)*

p value/*p vrednost*	Delta/*Delta*	Theta/*Teta*	Alpha/*Alfa*	Beta/*Beta*	Gamma/*Gama*
Cerebrum/*Veliki mozak*	0.0016	0.4913	0.0002	0.0072	< 0.0001
Cerebellum/*Mali mozak*	0.0075	0.1624	0.0378	0.0246	< 0.0001



Graph 1. Relative cerebellar spectral power in anesthetized rats (10 rats) and rats treated with aluminium (1.5 % solution of aluminium chloride hexahydrate per os, 10 rats).
Grafikon 1. *Relativna spektralna snaga malog mozga kod pacova pod anestezijom (10 jedinki) i pacova tretiranih aluminijumom (1,5% rastvor aluminijum-hlorid heksahidrata per os, 10 jedinki*)



Graph 2. Changes in the cerebellar relative spectral power – spontaneous activity in rats under anesthesia (10 rats) and in rats treated with aluminium (2 - 6 mg/kg i. p., 5 rats)
Grafikon 2. *Promena u relativnoj spektralnoj snazi malog mozga – spontana aktivnost kod jedinki pod anestezijom (10 jedinki) i kod pacova tretiranih aluminijumom (2 – 6 mg/kg i.p., 5 jedinki)*
Legend: L – left hemisphere, D – right hemisphere
Legenda: L – leva hemisfera, D – desna hemisfera

jective was to compare their spontaneous activity because recording was carried out under anesthesia. As a rule, the cerebrum is more susceptible to changes, while the cerebellum exhibits adaptive ability, and also has a role in the reparation of the damaged function - plasticity. During anesthesia, the cerebellum has a dominant delta activity, while during neurotoxicity, the delta activity fluctuates. The criterion for this change can be described by an increase in the relative spectral power within the delta range and by changing the FD of the neurotransmitting activity of the cerebellum. The role of the cerebellum in adaptability and plasticity is presented through spontaneous activity in the absence of stimuli and higher functional connections.

Spectral analysis shows changes in the relative spectral power across the frequency ranges. The present changes in relative spectral power are evident in all frequency ranges, indicating that anesthesia and aluminium have an effect on the entire neural network. Desynchronization of the rhythm is more exhibited in rats treated with aluminium than in anesthetized ones.

We presented the maximum change in relative spectral power in the group of rats treated with aluminium in frequency ranges, compared to the mean change in relative spectral power in the group of anesthetized rats.

Graph 1 shows the maximum change in individual rhythms of the relative spectral power in relation to the control group (anesthetized rats). All changes above the control level indicate intoxication. Both groups were recorded under anesthesia, with absence of sensory-motor reactions. The control group included 10 rats with stable anesthesia, and a minor change in the delta rhythm. The treated group also included 10 adult rats, exposed to solution of 1.5 % aluminium chloride hexahydrate per os, showing signs of intoxication. It appeared that there was a similar distribution of relative spectral power in the frequency ranges in the first and the second group of animals. It can be concluded that the spontaneous activity of the cerebellum cortex during anesthesia, as well as neurotoxicity, show the same distribution of relative spectral power, but under two different conditions of adaptation.

This kind of response in terms of changes in frequency ranges compared with spontaneous activity shows an increase in spectral power with symmetric distribution. This confirms the initial assumption that activity in a group of neurons was stimulated or inhibited simultaneously.

Graph 2 shows spontaneous activity of the cerebellum in rats treated with aluminium (2 mg/kg i. p.) during stable anesthesia (Zoletil). **Graphs 2 and 3** represent brain activity during anesthesia and neurotoxicity. The neurotoxicity of aluminium in anesthesia has a double effect. Anesthesia itself leads to an increase in relative spectral power within the delta range, while inhibition can affect glutamatergic transmission that occurs during toxicity. **Graph 3** shows the activity of the rat brain in the frequency ranges, and effects of anesthetic were described by standard deviation of the relative spectral power within the delta range**.** Changes in delta and theta ranges are related to plasticity, while in alpha and beta range they refer to higher sensory-motor performances.

Graph 4 shows an increase in the FD of electrocortical activity corresponding to the plasticity of the cerebellar cortex and the compensated toxicity, i. e. the adaptability of spontaneous activity of the cerebellum. The change in spontaneous activity of the cerebellum can be described by FD of electrocortical activity. An increase in FD of electrocortical activity during anesthesia suggests a change in the activity of the cerebellum, which is related to the inhibition of neurons and blocking of excitatory connections. This effect is reversible and indicates restoring the balance to reduce the effect of anesthesia. During aluminium intoxication, no changes were recorded, but the system oscillated around the balanced state. Even though anesthesia and aluminium intoxication has different mechanisms, their effects are expressed on the entire local neural network of the cerebellum. Under controlled conditions (anesthesia), variability and differences between activities of the left and the right hemisphere were recorded, which points to the plasticity and connectivity of the local networks of the cerebellar cortex. However, this feature is partially lost during aluminium intoxication, which was illustrated by FD values of electrocortical activity in **Graph 4**. During intoxication, there was a stable change of FD electrocortical activity in time, indicating that aluminium poisoning affects also the functional activity of the cerebellar cortex. But unlike the cerebrum, the cerebellum has a greater plasticity of neural network, so the reduction in FD of electrocortical activity is slightly smaller. This is related to inhibition due to the effect of anesthetics and glutaminenergic differences in the activity of these different parts of the brain. In relation to the control group of anesthetized animals, the increase in the relative spectral power within the delta range and the decrease in FD of electrocortical activity is the extent of intoxication of the cerebellum.

Discussion

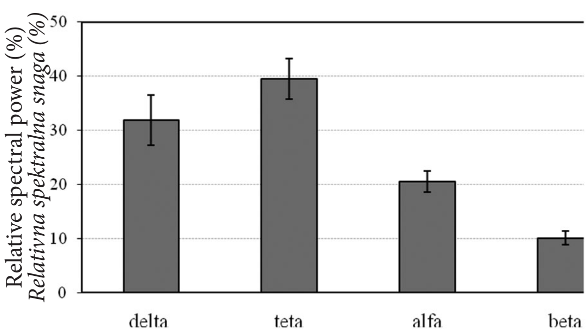
The cerebellar electrocorticographic activity is characterized by the presence of synchronized oscillations. Synchronization involves oscillation of two or more different structures at the same phase. There are two hypotheses on the role of synchronized oscillations: in testing conditions or in the preparation of motor activities [1].

In non-anesthetized rats, theta rhythm activity is dominant in cerebellum. It occurs in the granular layer and in an inert state of hemisphere it produces sensory information [11]. Theta activity of the granular cells occurs due to the repolarisation of the slow K^+ current [12]. K^+ and Na^+ current are sufficient for the occurrence of theta oscillations. Theta activity of the cerebellum is significant for synchronization and learning in the cerebellum. Theta oscillations of the cerebellum are also related to the activity of the neurons of the lower olive core or nucleus and its projections in the form of crawling fibres [13], as well as moss-like fibres that stimulate and inhibit grain cells.

In vivo stimulation of the lower olive nucleus induces oscillations over 10 Hz which are modulated by blockers of Ca^{2+} channels.

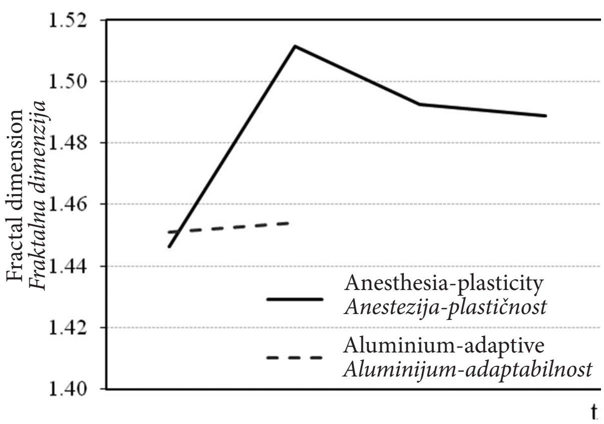
This activity is related to the Ca^{2+} transport [14]. The moss fibres stimulate the granular layer cells (granular and Goldgies) to oscillate with a frequency of 10 - 40 Hz. Oscillations depend on the excitation of the moss-shaped fibres during reducing the activation of parallel fibres [15]. During this process, desynchronization is caused by very weak activity of the moss fibres, a strong excitation of Goldgie cells, and activation of gamma-aminobutyric acid type A (GABA-A) receptors of granular cells. The mossy fibres are increasing the excitation of the grain cells, while Goldgie cells are inhibiting it. During desynchronization, the relation of excitation and inhibition is changing.

It has been shown that in lesions [16] and neurotoxicity [4] there is a desynchronization of the cerebellar activity. In case of lesions or neurotoxicity, the oscillatory activity is generated under the influence of input and output paths [5]. Spontaneous activity of the cerebellum is recorded in the absence of sensory-motor performances, and it describes the adaptive-plastic function in pathological conditions such as lesions or brain intoxication. Adaptability implies a change in the activity of the local cerebellar circuit, while plasticity implies a change in neurotransmitter activity under the influence of other structures. This activity in younglings involves compensation of changes and establishment a new balance, which has an adaptive value. In adult rats, the adaptability is associated with changes in the molecular and physiological neurotransmitter function which represents the plasticity



Graph 3. Average change in the biological rhythms of the cerebellum in 5 rats treated with aluminium (2 mg/kg i. p.) during anesthesia – relative spectral power in the frequency range

***Grafikon 3**. Prosečna promena bioloških ritmova malog mozga kod 5 pacova tretiranih aluminijumom (2 mg/kg i.p.) u uslovima anestezije - relativna spektralna snaga po frekventnim oblastima*



Graph 4. Fractal dimension of electrocortical activity in rats under anesthesia (15 rats) and treated with aluminium (2 mg/kg i. p., 11 rats) – plasticity and adaptive change

***Grafikon 4**. Fraktalna dimenzija elektrokortikalne aktivnosti kod pacova pod anestezijom (15 jedinki) i tretiranih aluminijumom (2 mg/kg i.p., 11 jedinki) – plastičnost i adaptivna promena* of the neurological network. It has been shown that occurrence of dark neurons in the cerebrum is due to intoxication and indicates a pathological condition, i. e. neurotoxicity [17].

In the model of aluminium neurotoxicity, changes caused by anesthesia are reversible, while toxicity implies a change in spontaneous activity – plasticity and adaptability. These changes imply that desynchronized activity strives to establish a balance in terms of increasing slow-wave/sporadic components. Particularly, an increase in the delta range is an indicator of neurotoxicity, while change in the delta/theta relation is a criterion of intoxication [18]. The FD of electrocortical activity during neurotoxicity has a lower value [19]. The change in FD of electrocortical activity in anesthetized rats and those treated with aluminium, describes rhythm desynchronization. An increase in FD of electrocortical activity in some rats in aluminium-treated group indicates a change in the oscillatory activity of the cerebellum. The increase is based on the change in the spontaneous cerebellar activity.

Conclusion

The cerebellum plays a role in compensating for neurotoxicity by changing spontaneous activity. The change in spontaneous activity indicates a dual role of the cerebellum: plasticity and adaptability. This kind of response implies an increase in fractal dimension of electrocortical activity which is otherwise reduced during neurotoxicity. The change in the delta rhythm in anesthesia or during intoxication is associated with a reduction in fractal dimension of electrocortical activity of the cerebellum. In case of reduction of fractal dimension of electrocortical activity, there is a change in the rhythm of spontaneous activity. It can be concluded that the fractal dimension of electrocortical activity can describe the role of the cerebellum in neurotoxicity (plasticity and adaptability).

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