ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Research Paper Acta Neurobiol Exp 2010, 70: 67–75

Spectral and fractal measures of cerebellar and cerebral activity in various types of anesthesia

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The features of rat cerebral and cerebellar electrocortical activity (ECoG) under different types of anaesthesia (nembutal, ketamine or zoletil) were examined by the distribution of spectral entropy across frequency bands of ECoG and by calculation of fractal dimension determined on the basis of Higuchi's algorithm. Spectral entropy, as a measure of activity, in the case of cerebrum had greater values than the spectral entropy of cerebellum in low frequency ranges, regardless of the type of applied anesthetic. Various anesthetics evoked different effects on spectral entropy of electrocortical activity: spectral entropy of delta range greatly dominated under nembutal anesthesia, while ketamine or zoletil appeared to affect the spectral entropy of higher frequency ranges. The pronounced effect of ketamine or zoletil anesthesia on spectral entropy of higher frequency was confirmed by the higher values of Higucihi's fractal dimension (FD) of ECoGs, with a tendency of higher FD values in cerebellar activity than cerebral activity.

Key word: cerebral activity, cerebellar activity, spectral entropy, fractal dimension, anesthesia, nembutal, ketamine, zoletil

INTRODUCTION

Interdisciplinary research on the cerebellum has extended the knowledge on cerebellar functions (reviewed by Ramnani 2006, Manto 2009). Traditionally, the cerebellum has been implicated in learning, coordination and control of fine-grained motor movements through the existence of reciprocal connections between cerebellum and primary motor cortex. It has become evident that the cerebellum has autonomic, cognitive and emotional functions based on cerebellar connections with the prefrontal cortex. It is still unclear how the cerebellum is involved in various pathophysiological conditions, what are the mechanisms by which long-distance coordination across different brain networks are maintained and how synchronous bursts play a role in coordinating activity in different frequency bands, as animals progress from sleep or anesthesia towards full consciousness (Hermer-Vazquez et al. 2009). On the other hand, it is well known that various anesthetics are used for producing blockade of sensory, motor, and autonomic as well as cognitive functions. The hypothesis that ECoGs/EEGs are in fact nonstationary and nonlinear in various pathophysiological conditions gives new opportunities for studying cerebellar versus cerebral activity. In the anaesthetized subject, the EEG still looks like a random waveform, but clearly a different random waveform from that seen in the conscious subject and GABA-ergic drugs cause predictable changes in EEG's bispectral indices and spectral entropy (Barnard et al. 2007). In our previous studies we noticed that slow power spectra of electrocortical activity predominated at the cerebellar level in nembutal anesthesia (Culic et al. 2005) and that fractal dimension values were greater at the level of cerebellar than cerebral cortex (Spasic et al. 2005) before as well as after acute brain injury. Our preliminary studies indicated that the mean values of parameters of cerebellar activity (fractal dimension and Hurst exponent), could be greater in wakefulness than in an anaesthetized state evoked by nembutal (Kekovic et al. 2009), and that distinct spectral changes of rat cerebral and cerebellar activity could occur

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Received 12 November 2009, accepted 07 January 2010

under various anesthesia regimens (Sekulic et al. 2009). The concept of information entropy (Shannon 1948) motivated us to suppose that the state of cerebrum and cerebellum, and information flow can be described by this parameter. Namely, under the influence of anesthesia, roughly speaking, the number of possible states of the brain is reduced, but this reduction is not the same in all frequency bands, which suggests introduction of entropy as a parameter of this distribution. According to contemporary understanding, cognitive brain activity takes place *via* transitional link groups of neurons, which resonate at different frequencies (Barbaro 2006). In this study we aimed to define changes ascribed to the particular anesthetic – nembutal, ketamine or zoletil, on the linear and non-linear parameters of cerebral and cerebellar electrocortical activity.

METHODS

Experimental animals, anesthesia and surgery

The experiments were performed on 15 male Wistar rats at 3.5 months of age. All procedures were done in accordance with the European Council Directive (86/609/EEC) and approved by the Ethical Committee for the care and use of laboratory animals at the Institute for Biological Research in Belgrade. The surgical and recording procedures were done during distinct state of anesthesia evoked by nembutal or ketamine or zoletil. Surgical and electrophysiological recording procedures were carried out on experimental animals divided in three groups (there were 5 rats in each group) after intraperitoneal administration of a particular anesthetic: Nembutal (Pentobarbitalnatrium; Serva,Germany) at the dose of 40 mg/kg or Ketamine hydrochloride (Rotex Medica, Germany) – 80 mg/kg or Zoletil 50 (Tiletamine: 50% + Zolazepam: 50%;Virbac SA, France) – 80 mg/kg. Each animal was mounted on a stereotaxic apparatus and round-shaped craniotomies were made over the parietal cerebral cortex (coordinates: 2.5 mm posterior to bregma and 2 mm left to the midline) and over cerebellar vermis (10.5 mm posterior to bregma and 1.5 mm left to the midline) for introducing silver/tungsten electrodes. Stable anesthesia was assessed by non-spontaneous foot movements and steady breathing rate; occasional on-line analysis of cerebral signals was also obtained during the recording procedure.

Recording procedure and data acquisition

The recording procedure was performed during stable anesthesia, within the period of 30–60 min after intraperitoneal administration of the anesthetic. Biosignals, local field potentials of the cerebral and cerebellar cortex (ECoG), were simultaneously recorded by epidurally positioned silver ball electrodes or, subdurally, superficially positioned tungsten micro-electrodes, with a ground electrode laid over the frontal bone and temporal muscles. Biosignals were amplified and filtered by a multichannel processor (Alpha-Omega Eng, Nazareth) with band pass filter from DC to 1 kHz and a 50 Hz notch. The biosignals were sequentially (every 7–10 min) stored after conversion from analog to digital form at the sampling rate of 256 Hz and each recorded sequence lasted 121 s. These sequences were filtered to avoid artifacts due to movements and other non-brain sources of electric activity (which could mostly occur at 61, 100, 107 and 121 Hz) for off-line spectral and fractal analysis.

Calculation of power spectra

Spectral analysis of biosignals (for more details in our study Culic et al. 2005) during sequences of 121 s (divided into epochs of 8 s), was obtained by Fast Fourier Transformation. Mean power spectra of biosignals during 15 epochs were obtained in five frequency ranges: delta (0.1–4.0 Hz), theta (4.1–8.0 Hz), alpha (8.1–12.0 Hz), beta (12.1–32.0) and gamma (32.1–128.0 Hz).

Spectral entropy

Assuming that the distribution of brain activity in the frequency domain may be critical for defining the spectral entropy (Fell et al. 1996, Misra et al. 2005, Srinivasan et al. 2005), we considered the properties of Fourier's power spectrum $P(f_i)$ and introduced a normalized power spectrum (Quiroga et al. 2000), according to the formula:

$$P_n(f_i) = \frac{P(f_i)}{\sum_{f_1}^{f_N} P(f_i)} \quad (1)$$

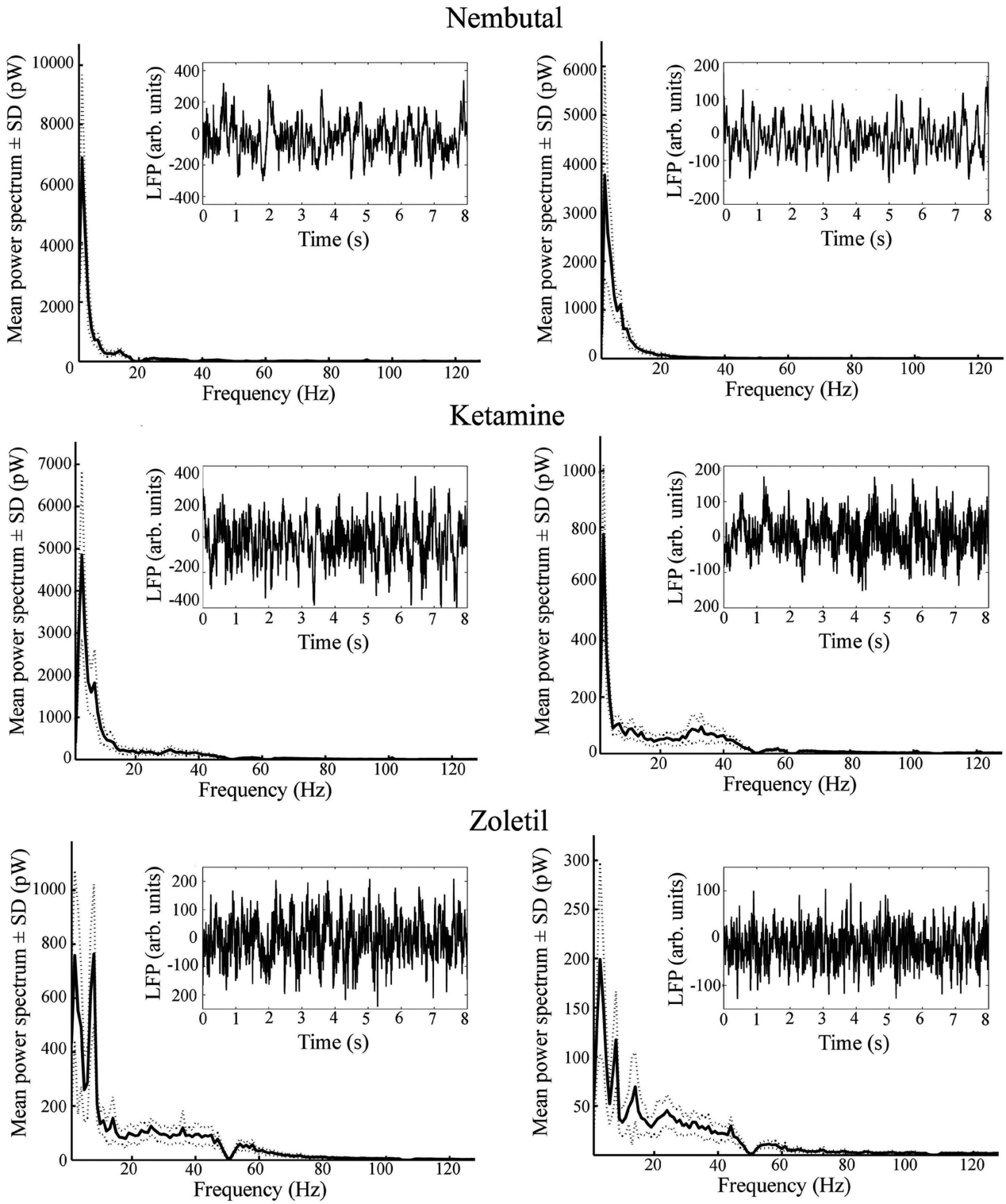

Fig. 1. Mean power spectra of simultaneously recorded cerebral (left column) and cerebellar (right column) activity in each of three rats under particular anesthesia: nembutal or ketamine or zoletil

It could be easily shown that holds:

$$\sum_i P_i(f_i) = 1$$

where index *i* runs over all frequency band. From this point of view, the normalized spectrum can be understood as the probability to find the system at a specific frequency. Accordingly, the spectral entropy of frequency band $-(f_1, f_2)$ is given by formula:

$$S_n(f_1, f_2) = \frac{\sum_{f_1}^{f_2} P(f_i) * \log(P(f_i))}{\log M} \quad (2)$$

and it is a measure of the total number of available states or rather, synaptic activity, within the band and terms *M* signify number of frequencies in that band. Spectral entropy for each of five already defined frequency ranges – delta, theta, alpha, beta and gamma – was calculated.

Calculation of fractal dimension

In this section, we shall briefly describe the famous Higuchi algorithm (Higuchi 1988, Spasic et al. 2005, Klonowski et al. 2006) which is one of the most accurate methods for the determination of fractal dimensions. For a discrete time series {x(1), x(2), ..., x(N)} a new time series were constructed, according to the formula:

$$X_k^m = \{x(m), x(m+1), \ldots\ldots, x(m + \\ + \text{int}[(N-m)/k]k)\}; \quad m = \{1,2,\ldots\ldots,k\} \quad (1)$$

where: *m* is the initial time, *k* is the–time interval, $k=\{1, 2, ..., k_{max}\}$ and *int*(*r*) is the–integer part of real number *r*. The length $L_m(k)$ was computed for each of the X_k^m series or curves according to the formula:

$$L_m(k) = \frac{1}{k}\left[\left(\sum_{i=1}^{\text{int}\left[\frac{N-m}{k}\right]} |x(m+ik) - x(m + \right.\right. \\ \left.\left. + (i-1)k)| \frac{N-1}{\text{int}\left[\frac{N-m}{k}\right]k}\right)\right] \quad (2)$$

and $L_m(k)$ was averaged for all *m*:

$$L(k) = \frac{\sum_{m=1}^{k} L_m(k)}{k} \quad (3)$$

giving the mean value of the curve length *L(k)* for each $k=\{1, 2, ..., k_{max}\}$. Finally, FD was determined from the plot *log(L(k)) versus 1/k* as a slope of the straight line. We used epochs of 200 experimental points (781 ms) and k_{max}=8 (Spasic et al. 2005). Individual FD values from all epochs were averaged in order to obtain a final FD value for a particular signal during a certain sequence (mostly of 121 s duration).

Statistical analysis

MANOVA was used to determine the significant differences in spectral entropy of five frequency ranges (0.1–4.0 Hz, 4.1–8.0 Hz, 8.1–12.0 Hz, 12.1–32.0 Hz and

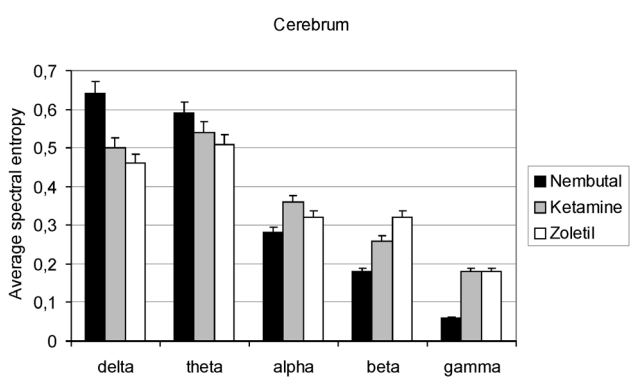

Fig. 2. Average spectral entropy of cerebral activity under three anesthesia regimens: nembutal or ketamine or zoletil (data of 5 rats in each regimen)

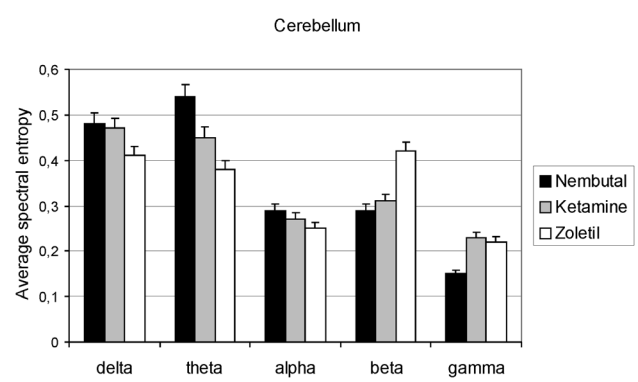

Fig. 3. Average spectral entropy of cerebellar activity under under three anesthesia regimens: nembutal or ketamine or zoletil (data of 5 rats in each regimen)

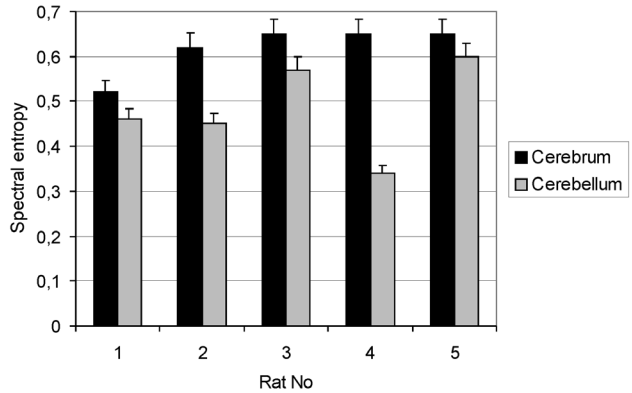

Fig. 4. The values of spectral entropy in delta frequency range in animals (5 rats in group) under the influence of nembutal anesthesia

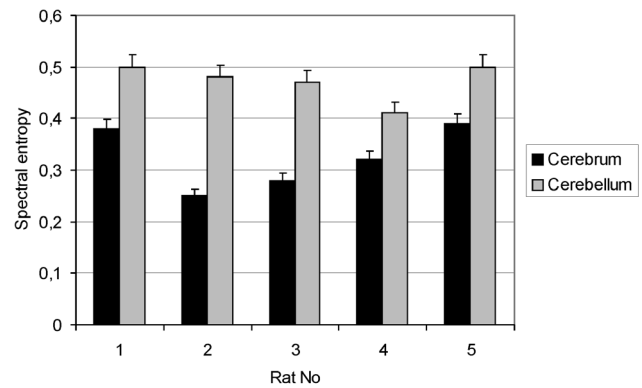

Fig. 5. The values of spectral entropy in beta frequency range in animals (5 rats in group) under the influence of zoletil anesthesia

32.1–128.0 Hz) at cerebral and cerebellar levels in different anaesthesia regimens. ANOVA was used to determine differences between spectral entropy of a particular frequency range under particular anaesthesia and *post hoc* LSD test was used for comparisons of particular mean measures. More specifically, we used a between-within multivariate (MANOVA) design where the particular anaesthesia regimen induced by a particular anaesthetic (nembutal, ketamine, zoletil) was the between – subject factor while the brain structure (cerebrum, cerebellum) was the within-subject factor. Dependent variables were spectral entropies in five frequency ranges.

RESULTS

The typical mean power spectra of cerebral and cerebellar activity obtained during different types of anesthesia is shown in Fig. 1. The first and logical step in signal analysis is their examination. By visual inspection of these pictures increase of mean power in the beta and gamma regions of cerebellum could be observed when ketamine and zoletil were applied, compared to nembutal. Also, there is a significant difference between the effects of these anesthetics in delta frequency band, where nembutal has a significant impact. These results served us as indicators of spectral properties of entropy as a measure of the activities of a certain frequency range.

The average values of spectral entropy of electrocortical activity at cerebral and cerebellar levels under three types of anesthesia through various frequency bands are shown in Figs 2 and 3. Increased value of spectral entropy, indicates increased activity and the effect of nembutal anesthesia is most apparent in delta range compared to two other anesthetic agents at both levels: cerebral and cerebellar, while there is a reverse situation in the area of higher frequency ranges. Zoletil and ketamine have greater influence in higher frequency bands when compared to nembutal anesthesia. By analyzing Fig. 3, it can be noticed that these effects are especially greater in the case of cerebellum, in beta frequency band.

For the purpose of detailed research of anesthetic agents, we discussed their effects within certain frequency bands and extracted the examples in which the effect of anesthetics could serve as a discriminative factor between cerebral and cerebellar response. We found that, under nembutal anesthesia, spectral entropy of cerebral activity in delta region was higher than spectral entropy of cerebellar activity and that low frequency ranges were dominant in cerebral activity (Fig. 4). There is another interesting property of theta frequency band regarding the effects of ketamine and zoletil where the values of spectral entropy in this frequency band are higher in cerebrum than in cerebellum. The similar situations are in alpha frequency band where the effects of ketamine and especially zoletil, are discriminative factors between cerebrum and cerebellum. In the following frequency range (beta), there is a significant change as zoletil (Fig. 5) and ketamine (Fig. 6) cause higher value of spectral entropy than nembutal. This is a sharp discriminant factor between cerebrum and cerebellum. In gamma frequency band, particularly, the effects of all applied anesthetics lead to higher spectral entropy in cerebellum than is cerebrum. Statistically significant

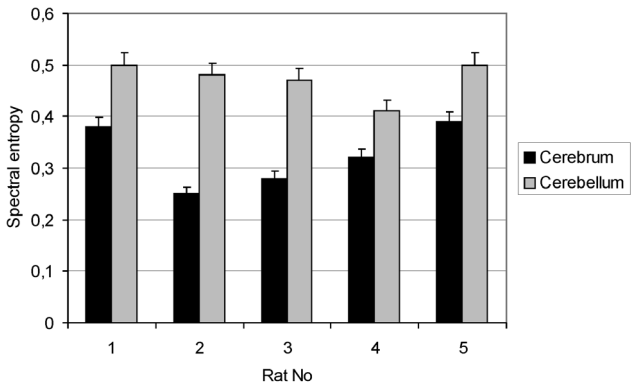

Fig. 5. The values of spectral entropy in beta frequency range in animals (5 rats in group) under the influence of zoletil anesthesia

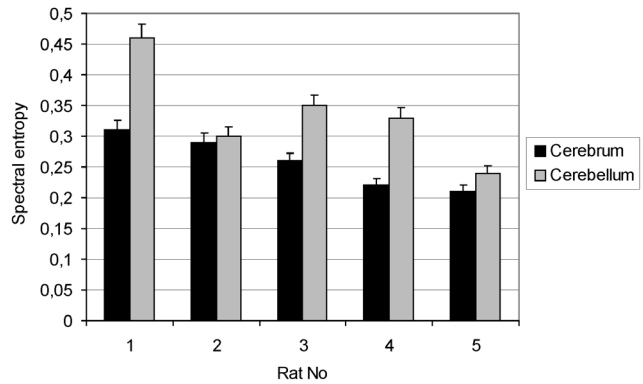

Fig. 6. The values of spectral entropy in beta frequency range in animals (5 rats in group) under the influence of ketamine anesthesia

influence of interaction between anaesthesia and brain structure on spectral entropy changes was obtained by between-within MANOVA test ($F_{8,12}$=3.27, P=0.017). This significant interaction between anesthesia and brain structure on spectral entropy changes occurred in beta frequency range (12.1–32.0 Hz), $F_{2,12}$=11.72, P=0.0015. Different type of anesthesia induced spectral entropy changes in 12.1–32.0 Hz at cerebral level and cerebellar level. There was an increase of spectral entropy at cerebral level, under zoletil anesthesia (P=0.01) compared to nembutal. At cerebellar level, ketamine and zoletil anesthesia compared to nembutal, induced significant increase in spectral entropy (P=0.006, P=0.00004). At the cerebellar level, zoletil anesthesia compared to ketamine, induced a significant increase in spectral entropy (P=0.01). We found by ANOVA where the uncorrelated variables were mean values of spectral entropy under different anesthetics in delta frequency band, the significant differences between nembutal and ketamine effects (F_1=14.6, P<0.019) and between nembutal and zoletil (F_1=14.93, P<0.018) in the case of cereberum. However, significant differences were not found between effects of different anesthetics in delta frequency band in the case of cerebellum.

This trend was followed by FD values (Fig. 7), which typically were greater at the cerebellar level than at cerebral, regardless of the type of applied anesthetic. It was already pointed out that the cerebellar activity was dominated by higher frequencies and was shown by strict sensitivity of FD values to high frequency activity. Also, in Fig. 7 it can be seen that due to the effects of ketamine or zoletil, the value of mean FD was higher than in the case of nembutal in both structures – cerebrum and cerebellum.

DISCUSSION

The interesting changes of cortical electroencephalogram occur during pentobarbital, ketamine and zoletil anesthesia which are commonly used in animal experiments. Our experimental study by using various measures of brain local field potentials shows for the first time that general suppression of neuronal activity caused by specific anesthetic can induce distinct spectral and complexity gradients of cerebral and cerebellar activity in adult Wistar rats. Concerning various anesthetics, effects of pentobarbital anesthesia differ clearly from ketamine-xylazine on somatosensory and brainstem auditory evoked responses (Goss-Sampson and Kriss 1991). Pentobarbital anesthesia induced an increase in relative power in alpha and beta bands and a decrease in the theta band, but the degree of these power variations was more marked in aged rats, while ketamine anesthesia increased relative power in the delta band and

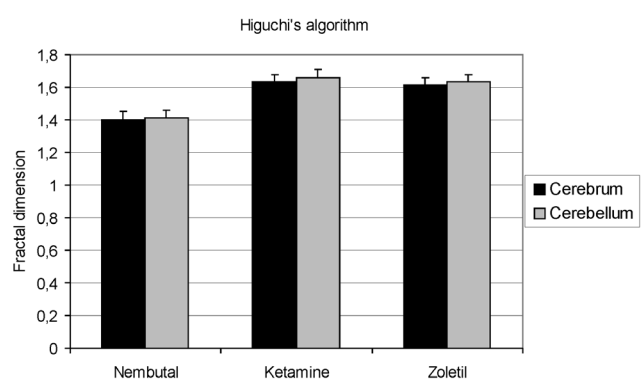

Fig. 7. Mean FD values of cerebral and cerebellar activity under particular anesthesia

decreased it in the theta band and these effects were more marked in aged rats than in the young ones (Fu et al. 2008). Keeping in mind that we have worked with adult rats, the effects of ketamine in our case fully agree with these results. Ketamine caused an increase of cerebral spectral entropy of 16% in delta range and the decrease of 16.9% in the theta frequency range. A similar situation occurred in the cerebellum, where there was an increase in the values of spectral entropy in the delta range (21.3%) and decrease in the values of theta range (11.8%). There exists another interesting experimental result concerning the effects of various anesthetics. Namely, experimental anesthesia regimens evoked by particular anesthetic – nembutal or ketamine or zoletil, modify in a distinct way the spontaneous neural outflow of the cochlea of the guinea pig (Sendowski et al. 2006).

It is also known that the brain generates many rhythmic activities, and cerebellum is not an exception (as reviewed by D'Angelo et al. 2009). Although the EEG of the cerebellum is not used in daily clinical practice, experimental analysis has revealed that the cerebellum, in humans, can express all series of rhythms encompassing the theta, alpha, beta, gamma and very high frequency bands (Gross et al. 2002, Dalal et al. 2008). These rhythms are likely to arise to a large extent from electric fields generated in the molecular layer (Isope and Barbour 2002, Cheron et al. 2008, Middleton et al. 2008), but the granular layer is likely to contribute as well to at least some of these rhythms (as reviewed by De Zeeuw et al. 2008). Extracellular field recordings in freely behaving animals have shown that large granular layer areas can oscillate in harmony demonstrating remarkable coherence in the 7–25 Hz frequency range (Hartmann and Bower 1998, Schnitzler et al. 2006). In the light of this discussion, we found that the effects of all three anesthetics in the cerebellum caused drastically reduced value of spectral entropy in beta range compared to the control signal. Possible explanation is inhibitory effect of anesthetics on granular and Purkinje cell layers. The questions remain: which network factors cause the cerebellum to generate particular internal rhythms, how does the oscillating cerebellum communicates with extracerebellar structures and what might the functions of these oscillations be (Buzsaki 2006, De Zeeuw et al. 2008). Paleocerebellum correlates at a weak to moderate level during different periods of SWD burst generation in WAG/Rij rats, particularly towards the end of SWD when an increased interhemispheric correlation between left fronto-temporal and right fronto-occipital cortical zones was found (Godlevsky et al. 2006). It is hypothesized by J. Ghajar and R.B. Ivry (2009) that a network encompassing prefrontal cortex, parietal lobe and cerebellum may be critical in the maintenance and timing of generating anticipatory neuronal activity that can synchronized with expected sensory information.

CONCLUSIONS

The results of our study indicate the diversity of effects of nembutal, ketamine and zoletil, where as the dependent variable appears to be the spectral entropy of cerebral and cerebellar activity. Based on values of this parameter for various frequency bands, we found that low frequencies dominated in both structures, regardless of the type of applied anesthetic. Nembutal induces largest activity in the delta and theta region of cerebrum, while in the field of higher frequencies, the situation is reversed in terms of domination of ketamine and zoletil. This fact was confirmed by the values of fractal dimension. Relative mean power spectra, spectral entropy and fractal dimension can be successfully used to describe not only cerebral activity but also the cerebellar activity in various states of consciousness and could be useful for improving diagnostic methodology although we are aware that consciousness is not generated by cerebellum.

ACKNOWLEDGEMENT

This study is supported by the Ministry of Science and Technological Development of Republic of Serbia (project 143021).

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