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Electrophysiological Study of Campbell Line Rats Before and After the Administration of Drugs

Elmar Mustafa Ogly Kasimov, Ulduz Faizi Kyzy Hashimova,
Andrey N. Ilnitskiy, Afet Nasib Kyzy Mamedzade and
Natavan Irshad Kyzy Alieva

Abstract--- *The study includes the evaluation of the total bioelectric activity of a,b,c waves of the electroretinogram (ERG) and mean values of the amplitude of b-waves in the retina of Campbell rats of different age before and after the administration of the drugs (Retinalaminum and Retinalaminum + Omk1). The study results showed that the administration of Retimalaminum and Retinalaminum + Omk1 to neonate rats led to a significant improvement in total bioelectric activity of the waves a,b,c of ERG. A significant increase in this parameter values was also observed in neonate rats after the combined administration of Retinalaminum + Omk1 in comparison with the group of rats that received only Retinalaminum. In adult rats, the administration of the abovementioned parameters improved the bioelectric activity of the waves a,b,c of ERG, but there were no significant differences between the administration of Retinalaminum and Retinalaminum in combination with Omk1 revealed. There were no significant data on the improvement of bioelectrical activity in senior rats after the administration of the drugs. The study of the mean values of b-wave in rats of different age revealed the same consistency as it was observed in the total bioelectrical activity according to ERG.*

Keywords--- *Retinitis Pigmentosa, ERG, Retinalaminum, OMK1.*

I. INTRODUCTION

Retinitis pigmentosa (RP) is a severe inherited progressing eye disease that primarily affects the photoreceptor layer and pigmented epithelium [4, 23]. RP affects humans of any age, primarily young people, and leads to the disabilities in the working-age population. RP is diagnosed based on the records of the progressing loss of photoreceptors function revealed by electroretinography [2]. Electroretinography (ERG) is aimed at early identification of ophthalmologic pathology, control of the effectiveness of the methods of treatment and therapy. Presently, ERG becomes widespread for detailed knowledge of the mechanisms of pathogenesis and functional signs of the development of RP [3, 10, 11, 21, 22].

It is known that the treatment of patients with inherited degenerations is a complicated task. The morbidity rate of numerous diseases of the retina is constantly decreasing due to the development of methods of prevention, early

Elmar Mustafa Ogly Kasimov, Doctor of Medical Sciences, Professor, Corresponding Member of National Academy of Sciences of Azerbaijan, National Ophthalmologic Center named after Zarifa Alieva, 15/32 Javadkhan Street, Baku, Azerbaijan. E-mail: oftal.jurnal@eye.gov.az

Ulduz Faizi Kyzy Hashimova, Doctor of Biological Sciences, Professor, Institute of Physiology named after A.I. Karaev, Azerbaijan National Academy of Sciences, 2 Sharifzadze Street, Baku, Azerbaijan. E-mail: lduz.hashimova@science.az

Andrey N. Ilnitskiy, Doctor of Medical Sciences, Professor, Autonomus Non-Commercial Organization "Scientific and Research Medical Center "Gerontology", 6 1st Aeroportovskaya Street, Moscow, Russia. E-mail: ilnitski@yandex.ru

Afet Nasib Kyzy Mamedzade, PhD of Medical Sciences, National Ophthalmologic Center named after Zarifa Alieva, 15/32 Dzhavadkhan, Baku, Azerbaijan. E-mail: mamedzade04@mail.ru

Natavan Irshad Kyzy Alieva, PhD of Medical Sciences, National Ophthalmologic Center named after Zarifa Alieva, 15/32 Javadkhan Street, Baku, Azerbaijan. E-mail: natavan7777@mail.ru

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diagnostics, and specific treatment but, in the case of blindness caused by RP, the problem remains acute [4, 23]. A literature review showed that the methods and means of treatment for RP are diverse and multidirectional [4, 5, 7, 15, 19]. Presently, specific methods of treatment are at the stage of development and clinical trials. Experimental medicine demonstrates promising results of the application of gene therapy, stem cells, and other therapeutic methods [5, 14, 13, 18, 20, 21]. In clinical practice, only supportive therapy is used that is aimed at slowing down the progression of the manifestations of this disease. For this purpose, Vitamin A containing drugs are administered that improve the trophism of the retina and other optical structures [1, 8, 9, 12]. The prognosis of RP is considered to be unfavorable because of a constant disease progression that leads to total blindness.

The aim of the present study was to evaluate the total bioelectric activity of the waves a,b,c of ERG and the average amplitude of the b-wave of the retina in rats of different age before and after the administration of the drugs (Retinalaminum and Retinalaminum + Omk1).

II. MATERIALS AND METHODS

The study included Campbell rats with experimental modeled pigmented degeneration of the retina. These are pale-hood rose-eyed homozygous rats with inherited retinal dystrophy and impairment of the specific phagocyte function of the retinal pigmented epithelium.

The experimental part of the study included the investigation of electrophysiological parameters (total bioelectrophysiological activity of a,b,c waves and the average amplitude of b-waves) in rats with ERG.

ERG is a leading method of the evaluation of the functional status of the retina and allows the specialists to reveal not only expressed dystrophic alterations in the retina but also diagnose biochemical and functional disorders that precede clinical manifestations of RP, which provided the reason for the choice of this method for the present study.

The registration of ERG was performed with a corneal contact electrode. The reference electrode was placed subcutaneously on the back of the neck. The total bioelectric activity of a,b,c waves was assessed with ERG. For the quantitative evaluation of the intensity of the response, the analysis of the maximum amplitude of ERG b-wave. Qualitative evaluation of other ERG components (a-wave and off-response) was not accounted because they were poorly expressed in the studied animals.

The study included 3 groups of rats divided by age: 148.0 ± 8.2 g neonate rats, 254.6±10.3 g adult rats aged 3.5±0.3 months, and 412.3±15.2 g senior rats aged 17.2±1.2 months. Each age group was divided into 2 subgroups. Rats from Subgroup I received parabulbar injections of Retinalaminum. Rats from Subgroup II received parabulbar injections of Retinalaminum and instillations of Omk1 for the monitoring of the effect of Retinalaminum in and a combination of drugs in dynamics during different periods of observation. The registration of the data was performed 7 and 14 days after the administration of the drugs. These rats were placed in the vivarium in comfortable temperature conditions (environmental air temperature 21°C). The daylight period was 12 hours. The animals received feed for rats and supplementary food (fruit and vegetable). Animals had free access to water in drinking tanks. Rats received food and water adlibitum. The cages were cleaned daily and disinfected weekly.

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For the evaluation of the significance of the obtained results in each group, Newman-Keuls test was used. The obtained results were statistically significant at $p<0.05$. For the evaluation of the significance of the results obtained in the groups of rats before the administration of the drugs in comparison with the groups of rats after the administration of the drugs, Dunnett test was used.

III. Results And Discussion

The authors evaluated the total bioelectric activity of ERG a,b,c waves in rats of different age in different time periods. Thus, before the administration of the drugs, in neonate rats, it was 88.6 ± 10.1 μV, which is explained by the fact that a decrease in bioelectric activity is observed at the age of 19 days after the birth [5]. 7 days after the administration of Retinalaminum, this parameter value was 111.2 ± 13.9 μV, at $p<0.05$ the difference was significant between the groups of rats of the same age before and after the administration of Retinalaminum in different time periods. 7 days after a combined administration of Retinalaminum + Omk1, this parameter value was 119.7±14.1 μV, at $p<0.05$ the difference was significant between the groups of the same age after the administration of Retinalaminum and after combined administration of Retinalaminum + Omk1 in different time periods (Table 1).

It should be noted that the obtained data on a significant increase of total bioelectric activity by 1.1 times in rats after a combined administration of Retinalaminum + Omk1 in comparison with a group of rats that received only Retinalaminum.

After the administration of Retinalaminum on Day 14, this parameter value was 126.3 ± 15.5 μV, at $p<0.05$ the difference between the groups of one age before the administration of the drugs and after the administration of Retinalaminum in different time period was significant; at $p<0.05$ the difference between the groups of one age after the administration of Retinalaminum on Day 7 and Day 14 was significant. After a combined administration of Retinalaminum + Omk1 on Day 14, the parameter value reached 128.4 ± 15.7 μV, at $p<0.05$ the difference between the groups of one age before the administration of the drugs and after a combined administration of Retinalaminum + Omk1 was significant on Day 14; at $p<0.05$ the difference between the groups of one age after the administration of Retinalaminum + Omk1 was significant on Day 7 and Day 14 (Table 1).

It should be mentioned that 14 days after the administration of the drugs, the authors obtained data on the total bioelectrical activity in rats after a combined administration of Retinalaminum + Omk1 in comparison with the group of rats that received only Retinalaminum but these data were insignificant. It should be highlighted that the administration of Retinalaminum and Retinalaminum + Omk1 to neonate rats leads to a significant improvement of the parameters according to ERG.

Before the administration of drugs, in adult rats, the total bioelectrical activity was 10.5 ± 3.8 μV, which was 8.4 times lower than in neonate rats, which can be explained by an age-related decrease in the total bioelectrical activity. On Day 7, after the administration of Retinalaminum, this parameter value was 15.4 ± 4.5 μV, at $p<0.05$ the difference between the groups of one age before the administration of the drugs and after the administration of Retinalaminum in different time periods was significant. On Day 7, after a combined administration of Retinalaminum + Omk1, this parameter value reached 17.3 ± 4.8 μV, at $p<0.05$ the difference between the groups of one age before the administration of the drugs and after a combined administration of Retinalaminum + Omk1 on

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Day 7 was significant; at $p>0.05$ the difference was insignificant between the groups of one age after the administration of Retinalaminum and after a combined administration of Retinalaminum + Omk1 in different time periods (Table 1).

It should be noted that the authors did not obtain data on a significant increase of the total bioelectrical activity in adult rats after a combined administration of Retinalaminum + Omk1 in comparison with the group of rats that received only Retinalaminum.

On Day 14, after the administration of Retinalaminum, this parameter value in adult rats was 16.5 ± 4.6 μV, at $p<0.05$ the difference was significant between the groups of one age before the administration of the drugs and after the administration of Retinalaminum on Day 14; at $p>0.05$ the difference was insignificant between the groups of one age after the administration of Retinalaminum on Day 7 and 14. On Day 14 after a combined administration of Retinalaminum + Omk1, this parameter value 18.6 ± 4.9 μV, at $p<0.05$ the difference was significant between the groups of one age before the administration of the drugs and after a combined administration of Retinalaminum + Omk1 on Day 14; at $p>0.05$ the difference was insignificant between the groups of one age after the administration of Retinalaminum + Omk1 on Day 7 and Day 14 (Table 1).

It should be noted that 7 and 14 days after the administration of the drugs, there was no difference in the total bioelectric activity. These data indicate the fact that patients with early stages of RP who received Retinalaminum had maximum significant improvement of the condition according to ERG.

In senior rats before the administration of the drugs, the total summed bioelectrical activity was 1.6 ± 0.4 μV, which was 55.4 times lower than in neonate rats, and 6.6 times lower than in adult rats, which is explained by a decrease in the total bioelectrical activity with aging. On Day 7 after the administration of Retinalaminum, this parameter value was 1.8 ± 0.5 μV, at $p>0.05$ the difference was insignificant in all the studied groups. On Day 7 after the administration of Retinalaminum + Omk1, this parameter reached 1.9 ± 0.6 μV, at $p>0.05$ the difference in the parameters was insignificant in all the groups (Table 1).

Thus, the authors did not obtain significant data on the improvement of bioelectrical activity in senior rats.

On Day 14 after the administration f Retinalaminum, this parameter in senior rats was 1.8 ± 0.5 μV, at $p<0.05$ the difference between the groups of one age was significant before and after the indication of Retinalaminum; at $p>0.05$ the difference in the parameters was insignificant in all the studied groups. On Day 14 after a combined administration of Retinalaminum + Omk1, this parameter reached 1.8 ± 0.5 μV, at $p>0.05$ the difference in the parameters was insignificant in all the studied groups (Table 1).

It should be noted that 7 and 14 days after the administration of the drugs, there was no difference in the total bioelectric activity. These data indicate that the administration of Retinalaminum to neonate and adult rats resulted in maximum improvement of bioelectrical activity according to ERG. However, in senior rats, the results were insignificant.

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Table 1: Total Bioelectric Activity of the Erg Waves a,b,c in Rats of Different Age in Different Time Periods (M±m, μV)

Rats age groups	Before (n=30)	Day 7		Day 14	
		Retinalaminum (n=30)	Retinalaminum + Omk1 (n=30)	Retinalaminum (n=30)	Retinalaminum + Omk1 (n=30)
Neonates	88.6 ± 10.1	111.2 ± 13.9*	119.7±14.1**, $^{\#}$	126.3 ± 15.5*, ^{o}	128.4 ± 15.7**, ^{oo}
Adults	10.5 ± 3.8	15.4 ± 4.5*	17.3 ± 4.8**	16.5 ± 4.6*	18.6 ± 4.9**
Seniors	1.6 ± 0.4	1.8 ± 0.5	1.9 ± 0.6	1.8 ± 0.5	1.8 ± 0.5

*p<0.05 – the difference is significant between the groups of one age before the administration of drugs and after the administration of Retinalaminum in different time periods

**p<0.05 – the difference is significant between the groups of one age before the administration of drugs and after the combined administration of Retinalaminum + Omk1 in different time periods

#p<0.05 – the difference is significant between the groups of one age after the administration of Retinalaminum and after the combined administration of Retinalaminum + Omk1 in different time periods

^{o}p<0.05 – the difference is significant between the groups of one age after the administration of Retinalaminum on Day 7 and Day 14

^{oo}p<0.05 – the difference is significant between the groups of one age after the administration of Retinalaminum + Omk1 on Day 7 and Day 14

The study of the mean value of the amplitude of b-way by ERG revealed the following data. Thus, in neonate rats before the administration of the drugs, this parameter was 36.8±1.2% of the norm, which is explained by a decrease in the b-wave amplitude at the age of 19 days old [5]. On Day 7 after the administration of Retinalaminum, this parameter was 40.7±1.8% of the norm, at p<0.05 the difference was significant between the groups of one age before the administration of the drugs and after the administration of Retinalaminum on Day 7. On Day 7 after a combined administration of Retinalaminum + Omk1 reached 45.9±2.1% of the norm, at p<0.05 the difference was significant between the groups of one age before the administration of the drugs and after a combined administration of Retinalaminum + Omk1 on Day 7; at p<0.05 the difference was significant between the groups of one age after the administration of Retinalaminum and after a combined administration of Retinalaminum + Omk1 on Day 7. It should be noted that the authors obtained data on a significant increase in the total bioelectrical activity by 1.1 times in neonate rats after a combined administration of Retinalaminum + Omk1 in comparison with a group of rats after the administration of Retinalaminum (Table 2).

On Day 14 after the administration of Retinalaminum, this parameter reached 48.6±2.3% of the norm, at p<0.05 the difference was significant between the groups of one age before the administration of the drugs and after the administration of Retinalaminum on Day 7; at p<0.05 the difference between the groups of one age after the administration of Retinalaminum + Omk1 on Day 7 and 14. On Day 14 after a combined indication of Retinalaminum + Omk1, this parameter value reached 49.6±2.4% of the norm, at p<0.05 the difference was significant between the groups of one age before the administration of the drugs and after a combined administration

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of Retinalaminum + Omk1 on Day 14; at $p<0.05$ the difference was significant between the groups of one age after the administration of Retinalaminum + Omk1 on Day 7 and 14. It should be mentioned that 14 days after the administration of the drugs, the authors obtained data on the increase in the amplitude of b-wave in rats after a combined administration of Retinalaminum + Omk1 in comparison with the group of rats that received only Retinalaminum, however, this increase was insignificant, $p>0.05$ (Table 2). It should be highlighted that the administration of Retinalaminum and Retinalaminum + Omk1 in neonate rats leads to a significant improvement of the parameters according to ERG.

Before the administration of the drugs, in adult rats, the mean values of the b-wave amplitude were 14.5±0.7% of the norm that was 2.5 times lower than in neonate rats, which is explained by a decrease in the total bioelectrical activity with aging. On Day 7 after the administration of Retinalaminum, this parameter value was 15.9±0.8% of the norm, at $p>0.05$ the difference in the parameters was insignificant between the groups of one age before the administration of the drugs and after the administration of Retinalaminum on Day 7. On Day 7 after a combined administration of Retinalaminum + Omk1 reached 17.7±1.2% of the norm, at $p<0.05$ the difference between the parameters was significant between the groups of one age before the administration and after a combined administration of Retinalaminum + Omk1 on Day 7; at $p>0.05$ the difference was insignificant between the groups of ane age after the administration of Retinalaminum and after a combined administration of Retinalaminum + Omk1 on Day 7 (Table 2).

It should be noted that there were no data on a significant increase in the total bioelectrical activity in rats after a combined administration of Retinalaminum + Omk1 in comparison with the group of rats that received only Retinalaminum.

On Day 14 after the administration of Retinalaminum, in adult rats, this parameter was 16.9±1.0% of the norm, at $p>0.05$ the difference in the parameters was insignificant between the groups of one age before the administration of the drugs and after the administration of Retinalaminum on Day 14, at $p>0.05$ the difference was insignificant between the groups of one age after the administration of Retinalaminum on Day 7 and Day 14. On Day 14 after a combined administration of Retinalaminum + Omk1, this parameter reached 17.8±1.2% of the norm, at $p<0.05$ the difference was significant between the groups of one age before the administration of the drugs and after a combined administration of Retinalaminum + Omk1 on Day 14, at $p>0.05$ the difference between the parameters was insignificant between the groups of one age after the administration of Retinalaminum + Omk1 on Day 7 and Day 14. It should be mentioned that on Day 7 and Day 14 after the administration of the drugs, there was no significant difference between the mean values of b-wave amplitude (Table 2).

In senior rats before the administration of the drugs, mean value of b-wave amplitude was 6.8±0.5% of the norm that was 2.5 times lower than in neonate rats and 2.1 times lower than in adult rats, which is explained by a decrease in the total bioelectrical activity with aging. On Day 7 after the administration of Retinalaminum, this parameter was 6.8±0.5% of the norm, at $p>0.05$ the difference between the parameters was insignificant in all the groups. On Day 7 after a combined administration of Retinalaminum + Omk1, this parameter reached 6.9±0.6% of the norm, at $p>0.05$ the difference between the parameters was insignificant in all the groups (Table 2).

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Thus, there were no significant data on the improvement of the mean values of b-wave in senior rats.

On day 14 after the administration of Retinalaminum, in senior rats, this parameter value was 6.7±0.4% of the norm, p>0.05 the difference between the parameters was insignificant between the groups of one age before the administration of the drugs and after the administration of Retinalaminum on Day 14, at p>0.05 the difference between the parameters was insignificant in all the groups. On Day 14 after a combined administration of Retinalaminum + Omk1, the parameter remained within 6.7±0.4% of the norm, at p>0.05 the difference was insignificant in all the groups (Table 2).

It should be noted that on Day 7 and Day 14 after the administration of the drugs, there was no significant difference between the values of b-wave amplitude.

Besides, it should be highlighted that activation of natural protective mechanisms was observed only in neonate rats after the administration of Retinalaminum, which was expressed as an improvement of electrophysiological parameters at the end of the period of observation.

Table 2: Mean Values of b-wave Amplitude in Rats of Different Age in Different Time Periods (M±m, %)

Rats age groups	Before (n=30)	Day 7		Day 14	
		Retinalaminum (n=30)	Retinalaminum + Omk1 (n=30)	Retinalaminum (n=30)	Retinalaminum + Omk1 (n=30)
Neonates	36.8±1.2	40.7±1.8*	45.9±2.1$^{**,\#}$	48.6±2.3^{*,o}	49.6±2.4^{**,oo}
Adults	14.5±0.7	15.9±0.8	17.7±1.2**	16.9±1.0	17.8±1.2**
Seniors	6.8±0.5	6.8±0.5	6.9±0.6	6.7±0.4	6.7±0.4

*p<0.05 – the difference is significant between the groups of one age before the administration of drugs and after the administration of Retinalaminum in different time periods

**p<0.05 – the difference is significant between the groups of one age before the administration of drugs and after the combined administration of Retinalaminum + Omk1 in different time periods

#p<0.05 – the difference is significant between the groups of one age after the administration of Retinalaminum and after the combined administration of Retinalaminum + Omk1 in different time periods

^{o}p<0.05 – the difference is significant between the groups of one age after the administration of Retinalaminum on Day 7 and Day 14

^{oo}p<0.05 – the difference is significant between the groups of one age after the administration of Retinalaminum + Omk1 on Day 7 and Day 14

During the present study, the authors revealed the changes in the parameters by means of ERG, which is the most significant method in the study of RP. According to foreign authors, the analysis of the form of the ERG curve using Fourier transformation allowed the authors to establish that on the 20th day after the birth, in Campbell rats, the amplitude of a-waves and b-waves increased along with the brightness of the stimuli. On Day 30, the amplitude of b-waves in Campbell rats was much lower than in Winstar rats and it did not change with the increase in the brightness of the stimuli [16, 17]. According to Khavinson et al, Campbell rats from the control group had a sharp decrease in the bioelectrical activity on 23rd – 35th day, and by the 53rd day, ERG was not registered in any of the animals. Under the influence of the studied tetrapeptide, the rats had an increase in the ERG values. In the main

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group, from the 23rd day, it remained at a relatively high level and only from the 41st day, the amplitude started to decrease slowly. Thus, by the 41st day, the amplitude in the main group exceeded the control by 2.8 times [7].

The authors revealed that the administration of Retinalaminum + Omk1 in neonate rats led to a significant increase in the total bioelectrical activity of ERG a,b,c-waves. There was a significant increase by 1.1 times in the total bioelectrical activity of neonate rats after a combined administration of Retinalaminum + Omk1 in comparison with the group of rats that received Retinalaminum only. It should be mentioned that there were no significant differences in this parameter in adult rats. There were no significant differences in the improvement of bioelectrical activity in senior rats after the administration of the specified drugs in senior rats either. These data indicate that the administration of Retinalaminum to neonate rats with RP provides maximum significant improvement according to ERG.

The study of the mean amplitude of ERG b-waves revealed the same consistency as the study of the total bioelectrical activity. Besides, it should be highlighted that activation of natural protective mechanisms of the organism was observed only in neonate rats after the administration of Retinalaminum, which was expressed as an improvement of electrophysiological parameters at the end of the period of observation.

Experimental models of the study of the effect of Retinalaminum on the retina of rats were discussed in a number of publications [6, 7, 8, 9]. Thus, according to Khavinson et al, the administration of Retinalaminum led to a significant increase in the amplitude of ERG b-wave in comparison with the control. The therapeutic effect of Retinalaminum was observed in animals with an average damage of the retina already on the 15th day of the observation, reaching its maximum by the 35th day. The amplitude of ERG b-waves in the test animals during this period reached 80% from the background and was almost 2 times higher than in the control group. The positive effect of Retinalaminum was observed also in cases of severe damage to the retina [8]. All these data agreed with the obtained results and proved the positive effect of Retinalaminum on the retina of the rats.

IV. CONCLUSION

The administration of Retinalaminum to Campbell rats exerted positive effect on the retina, which is proved by a significant improvement of the total bioelectrical activity of ERG a,b,c-waves. A combined administration of Retinalaminum + Omk1 provided a more expressed positive effect. But it should be noted that maximum positive effect of these drugs expressed in neonate rats.

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