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PROBLEMS OF MODELING LOW-INTENSITY ELECTRORETINAL SIGNAL FOR ASSESSING THE RISKS OF NEUROTOXICATION

Abstract. Assessing the risks of neurotoxicity of the human body caused by the negative influence of free radicals of nanostructures, using electroretinography with low intensity of light irritation, is one of the most promising modern electrophysiological methods. However, there are challenges in modeling such a test low-intensity retinal response, caused by unknown or hidden effects of toxins on the human organism, making it difficult for an expert system to assess such risks.

The development, creation and use of new materials leads to increased risks of environmental pollution and human organism, which requires timely diagnosis and treatment [1]. Among the diseases, a special place is occupied by neurotoxicity caused by chemical factors. Industrial chemicals that affect the nervous system include: metallic mercury, manganese, arsenic compounds, tetraethyl lead, etc. Neurotoxicity is a toxic encephalopathy, in which neurological disorders are dominated by a progressive insufficiency of peripheral hemodynamics.

Syndrome of toxic-hypoxic encephalopathy is considered as a functional failure of the central nervous system, as a result of the combination of metabolic, hemodynamic, morphological changes in the brain tissues with chemical lesion.

It develops under the influence of neurotoxins – chemical compounds that are in the body in an amount that is capable of breaking the functions of vital organs and creating a danger to life. Intoxication, or poisoning, leads to a pathological condition caused by a violation of chemical homeostasis due to the interaction of the toxin with the organism.

Substances that may cause intoxication are divided into:

1) industrial poisonous substances;
2) poisonous chemicals (pesticides);
3) medicines;
4) household chemicals;
5) biological, plant and animal poisons;
6) fighting poisonous substances, etc. [2].

Among the diseases, a special place is occupied by neurotoxicity caused by chemical factors. In addition, toxicants can selectively affect any system of the body or organs. Since, under the influence of these toxins, the brain is primarily affected [3], the spread of acute and chronic neurotoxicosis is a major problem as clinical toxicology, occupational medicine, neurology, and medicine as a whole.

Objective and subjective methods of research are used to study the state of retina as an indicator of the influence of toxins on the human body. To subjective include psychophysical tests: the Purkinje test, laser interference, Medoc's sticks, recognition of two points, etc. However, subjective tests do not provide enough information to diagnose a patient's condition. Among the objective methods of research complementary to psychophysical tests, distinguish between ultrasound and electrophysiology.

The basic methods of ultrasound diagnostics of the eye include: one-dimensional echography (A-method), two-dimensional echography (acoustic scanning, B-method), ultrasound three-dimensional echography, energy dopplerography and ultrasound duplex scanning. However, even with low energy of ultrasound radiation, there is an additional invasiveness and a negative effect on the patient.

Therefore, for the reliable diagnosis and localization of the causes of the disease, electrophysiological methods based on the analysis of bioelectric signals from the studied parts of the visual system are the most promising ones.

Among the electrophysiological methods of the study are the following methods for assessing the functional state of the visual analyzer: the determination of electrical sensitivity of the optic nerve, electrooculography (EOG), electroencephalography (together with the registration of visual stimulated brain cortical potentials) and electroretinography. The founder of the clinical electrophysiology of the organs of vision is the Swedish ophthalmologist G. Karpe, who used contact lenses for research in 1945. His work was based on the development of Riggs. A large amount of work in the direction of fixing electroretinography and study of electroretinosignal, which is a graphical representation of the electrical reaction of the set of cellular elements of the retina of the eye to external light irritation, was carried out by the Swedish physiologist R. Granit.

In particular, it was found that mercury intoxication shows a decrease in the thickness of the retina in the area of the fovea, which indicates the development of dystrophic changes in it [4]. As a result of the research, inhibition of retinal bioelectric activity was detected in the form of increasing the threshold of electrical sensitivity, lengthening the latent recovery time, and reducing the morphological parameters (Fig. 1).

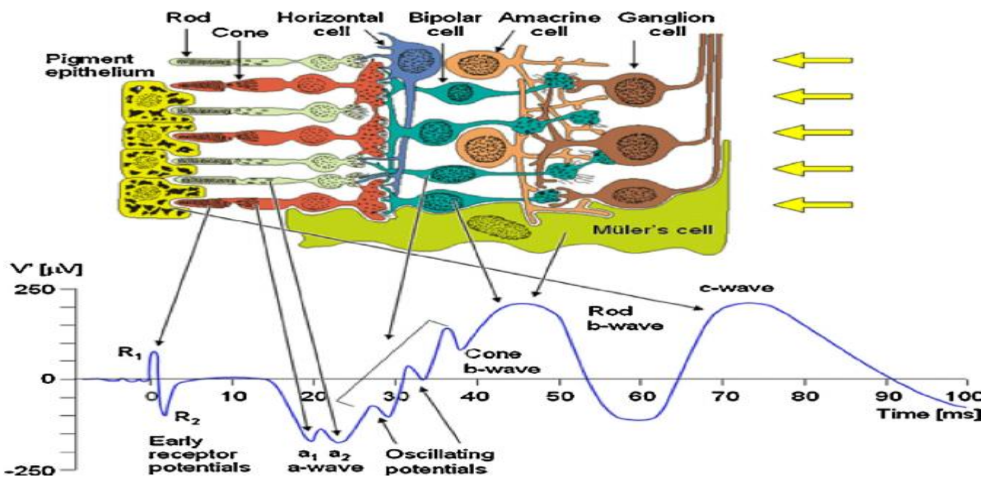


Fig. 1. Retina structure and sources of potential of ERS [5]

From studies of the group of applied physics doc. Shamshinova A.M. etc., found that the b-wave of electroretinogram (ERG) is the most sensitive to toxins and the value of the parameters of the ERS, depends on the intensity of the light stimulus [6].

Therefore, when the intensity of light irritation decreases, there is a greater chance of accurately registering the b-wave. To determine the intensity range of light irritation, the following criteria for the registration of ERG is a prerequisite:

I. threshold value of the logarithm of intensity of irritation, which improves the results of ERG registration;
II. determining the maximum value of the amplitude of the b-wave.

Accordingly, the level of irritation of the visual system (retina) increases in proportion to the logarithm of the intensity of light. In this case, the accuracy and resolution of the registered electroretinosignal increases (Weber-Fechner's law) [7]. Such studies did not have a prospect for selecting a standard electrolyte signal when conducting research with high energy of light irritation (in the range from 3 to 30 $cd \cdot s \cdot m^{-2}$) [8] .

High energy of light irritation allows to detect significant violations of the functioning of the visual analyzer, but it has a number of significant disadvantages:

1) the eye rejuvenates considerably;

2) the need for multiple ERS registrations (for the application of coherent filtration);

3) as a result, the length of the procedure increases significantly;

4) there is no possibility of displaying small morphological changes in the ERS, which is important for modern medicine [9] and [10].

Therefore, to reduce the negative effects of standard electroretinography, the decrease in the intensity of light irritation is used. Possibility of electroretinography with a significantly reduced energy of light irritation due to the peculiarity of the structure of the eye.

The maximum light sensitivity at a wavelength of 505-510 nm (blue-green light), for the reaction to light it takes from 43 to 48 quanta of light, but since the light flux passes through the optical environment of the eye, for the emergence of a low intensity electroretinosignal it is necessary that much more quanta be reached on the retina - up to 50-150 quanta of light. In view of this, in medical practice, the use of electroretinography with ultra-low energy of light irritation has been substantiated. The main advantages of quantum electroretinography are:

a) early diagnosis of changes in the functional state of the human body (in particular, in neurotoxication);

b) low energy of light irritation (from 10^{-3} to 10^{-4}) leads to decrease of invasiveness;

c) shortening the duration of the procedure, due to a significant reduction in eye rejuvenation time.

However, this will require the study of light stimulation (photostimulants) to reduce the intensity or exposure of light irritation, and the experimental reception of low-intensity ERS. The standards of ISCEV indicate the intensity of light stimuli for electroretinography studies. However, these standards are based on the use of gas-discharge xenon lamps (Grass PS-22, lamp PST-2100), while units of light stimulation measurement are adapted to the technical features of gas-discharge xenon lamps.

The first two methods have a significant disadvantage, due to the fact that the reduction of electrical parameters can only be to a certain limit. Further, the reduction of their light flux is impossible due to the internal structure and peculiarities of the physics of the transition of electrons through the p-n-junction. Therefore, it is promising to use PWM- modulation of the power supply of the LED.

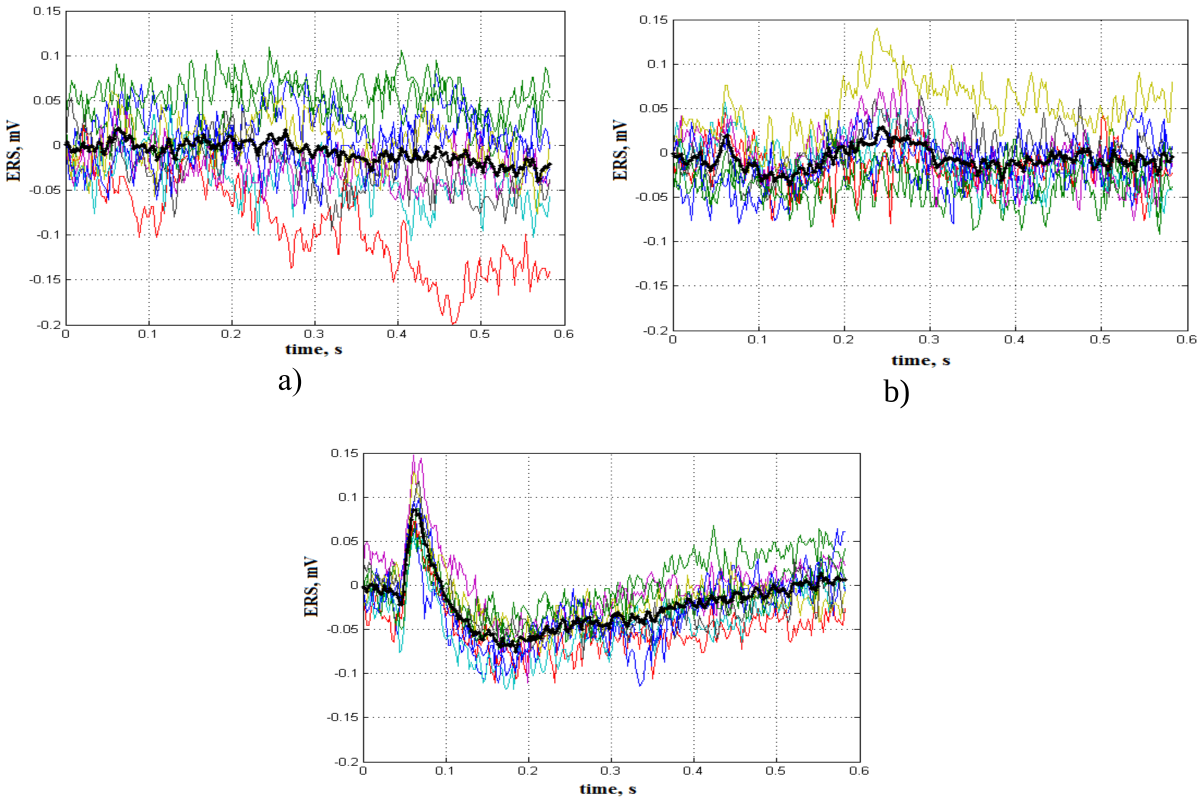
Summary table of parameters of the LED photo stimulator on the basis of the PWM modulator of power LED 3528

Switch position on PWM modulator	0	1	2	3	4	5	6	7	8	9	10
E(lux)	859	1847	4904	9044	14044	27276	24522	29808	35573	40732	41847
$t_i(ms)$	–	2,83	5,03	6,93	–	10,6	–	–	–	–	16,60
D, %	1	10	20	30	40	50	60	70	80	90	97
$H(lux \cdot s)$	–	0,522	4,933	18,802	–	144,56	–	–	–	–	673,82

In order to obtain an ERS with a reduced intensity of light irritation in a wide range of values, the ophthalmology system *DCSO-01* has been improved, with 250 samples with a quantization period Tq = 2.336 *ms* (sampling rate f_s = 428 *Hz*) and a predetermined number of registrations.

ERS is selected from the eye of a rabbit in a wide range of stimulus energies. As a source of irritation, a white LED (smd 3528) was used, the energy (*E*) of the radiation (stimulus) of which was given by three components: pulse cleft (*D*), magnitude and duration of direct current.

Such a method of forming the energy of the stimulus allows to provide a wide range of values $mcd \cdot s$ (Fig.2.a – c).



a) b) c)

Fig.2 ERS at different levels of intensity of light irritation:
a) I_{st} = 0.1 $mcd \cdot s$; *b)* I_{st} = 1.9 $mcd \cdot s$; *c)* I_{st} = 10.5 $mcd \cdot s$.

In order to reduce the noise of the ERS, the ERS ensemble was registered from 16 implementations with fixed energy of the stimulus followed by its averaging:

$$x_c(nT_q) = \frac{1}{16}\sum_{i=1}^{16} x_i(nT_q),$$

where $x_i(nT_q)$ — implementation of ERS, $x_c(nT_q)$ — averaged ERS for the given stimulus energy, nT_q — discrete time, *i* — implementation number.

The results are shown in *Fig. 2*, where the bold curve is depicted $x_c(nT_q)$, but thin — $x_i(nT_q)$.

During the experiment, more than 5000 ERS implementations were registered at different intensities of the light stimulus, but the resulting ERS when reducing the intensity of light irritation requires further elaboration and further research.

Conclusion. The analysis showed that in conditions of increasing the negative influence on the human body, the accuracy and resolution of standard electroretinography is not sufficient to detect the risks of neurotoxicity (detection of neurotoxicity, evaluation of their type, quantitative and qualitative characteristics, etc.).

Therefore, in order to diagnose the state of the visual analyzer, the most promising is the use of electroretinography with a reduced intensity of light irritation. The following results are obtained:

1) The functioning of the visual analyzer and the manifestation of sensations from the effects of stimuli (light stimulus) is explained by the Weber-Fechner empirical psychophysical law, therefore, to increase the accuracy and resolution (to detect the risk of neurotoxicity) reduce the energy of light irritation.

2) A pilot model for reducing the intensity of the light stimulus based on the PWM modulation of the LED power supply was created. This allowed to reduce the level of light irritation to 0.522 $lux \cdot s$, compared to the standard stimulation of electroretinography (Grass PS-33) – 59 $lux \cdot s$.

3) Experimentally, an ERS with a reduced intensity of light irritation has been obtained in a wide range of values $mcd \cdot s$, and the need for further elaboration of ERS for assessing the risk of neurotoxicity has been established.

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