THE INFLUENCE OF DELTALYCYN AND TRANSCRANIAL CEREBELLAR STIMULATION UPON RECOVERY OF RETINA AFTER PHOTO STRESS IN PATIENTS WITH DIABETIC RETINOPATHY

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THE INFLUENCE OF DELTALYCYN AND TRANSCRANIAL CEREBELLAR STIMULATION UPON RECOVERY OF RETINA AFTER PHOTO STRESS IN PATIENTS WITH DIABETIC RETINOPATHY (Abstract)  

Aim: The characteristics of visual evoked potentials (VEP) have been studied in diabetic patients with and without diabetic retinopathy.  

Material and methods: Magnetic impulses (2.0 Tl at the height of impulse) have been delivered to the cerebellar surface transcranially using the “Neuro-MS/D”, (Russia Federation). Delta-sleep inducing peptide (“Deltalycyn”, “Biopharma”, Russia Federation) was intranasally delivered in 30 min before photostress. Afterwards VEP have been registered every 20 s from the moment of photo stress during one minute.  

Results: An increase of the latency period and a reduction of the VEP amplitude have been recorded in the period following photo stress exposure of the macular part of the retina. The VEP characteristics restored to the initial level in 73.5± 3.3 s from the photo stress moment in the control group; while in diabetic patients with retinopathy this index was 137.2±11.3 s. In the presence of cerebellar transcranial magnetic stimulations (2.0 Tl, 20 impulses) the VEP amplitude depression was less pronounced, and the restoration period of the VEP characteristics shortened to 110.3± 12.7 s, while in deltalycyn treated patients restoration was observed in 95.1± 6.8 s. Under condition of combined usage of deltalycyn and TMS period of restoration of VEP was shortened up to 82.5± 6.5 s.  

Conclusions: Retinopathy development is linked to prolonged VEP latency period (P100), lowering of the N75-P100 amplitude, as well as to enlargement of the recovery period of the retina’s functional capacity in patients suffering from the diabetes mellitus in the presence of photo stress. Superlatively administered deltalycyn and cerebellar transcranial magnetic stimulation facilitates a faster recovery of the retina’s functional capacity in response to photo stress in diabetic patients with retinopathy.  


Keywords: DIABETIC RETINOPATHY, VISUALLY EVOKE POTENTIAL, DELTA-SLEEP INDUCING PEPTIDE, CEREBELLAR TRANSCRANIAL MAGNETIC STIMULATION

Diabetic retinopathy is one of the causes of development of the acquired blindness at the heart of which are the microcirculatory bloodstream impairment, increased vascular walls permeability, and vascularisation development that lead to the retinal detachment (1, 6). It has been established lately that retinopathy pathogenesis is linked to the activation of lipid peroxidation and to the increased concen-
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Intraration of proinflammatory cytokines in the retinal structures (6). Hence, methods based on usage of drugs with antioxidant mode of action are justified for the usage in patients suffered from diabetic retinopathy (2, 6). On the other hand, raising the neuronal brain tissues activity by means of transcranial stimulation in cerebellar zone is resulted in the retinal improvement in diabetic patients (4), and such an effect might be justified by activation of antioxidant potential of brain tissue (1).

Till the last time there were not investigations on effects of delta sleep-inducing peptide (DSIP) upon functional state of retina in patients suffered from diabetes retinopathy. Meanwhile DSIP is regarded as a compound with pronounced antioxidant and neuroprotective properties (5).

Therefore the objective of this research was studying of the recovery process of the retina’s functional activity in patients suffering from the diabetes retinopathy following a photo stimulation (photo stress) test (7) performed under conditions of DSIP – based drug – deltalyryn administration along with of cerebellar transcranial stimulation (4, 8).

MATERIAL AND METHODS

15 practically healthy individuals (the mean age 32.1± 3.6 years old) and 30 insulin-dependent diabetics (the mean age 30.9± 3.7 years old) were observed in this research.

All subjects provided written consent to research conduction. All investigations have been performed in accordance to ethics demands of commission on ethics at Odessa National Medical University (ON-MedU Animal Care and Ethics Committee, 2008/84).

By selecting the control group the following criteria were adhered to: the intraocular pressure less than 21 millimeters of mercury, preserved acuity of vision, unaltered visual field, and absence of eye diseases and neurological disorders. For the diabetics the criteria were as follows: the intraocular pressure less than 21 millimeters of mercury, correctable acuity of vision (more than 7/10), as well as absence of signs of the proliferative retinopathy, which was established by means of fluorangiography (4, 7). This method allowed us to compose the group of 30 patients with mild and severe proliferative retinopathy formed the third to fifth level groups in accordance to classification after (7).

While conducting the research the patients were observed in a dark and sound-proof room. Before recording the visually evoked potential (VEP) each subject has been adapting to the light intensity for 10 minutes till the moment, when the pupil diameter became equal to 3 mm. The level of the background screen glow was 5 cd/m^2.

VEP was recorded using the adopted technology (9). The visual stimuli – chess pattern – had the contrast degree 70% and the mean luminescence degree 110 cd/m^2, while the contrast reversion was carried out with a frequency two times per second. A subject was placed at a distance 114 cm from the screen center, what allowed a 15-seconds acceptance angle of separate pattern elements, and a 25 acceptance angle of the screen height. Only the right eye of all patients was tested, while the left one remained closed (4, 9).

The electrodes were placed at points Oz (the active electrode) and Fpz – the reference (recording) electrode; the grounding was fixed on the left arm.

The interelectrode resistance was set at 3 kOhm. The bioelectric signals were amplified (by 20,000 times); the signal transmission band comprised 1-100 Hz,
after which the signals were averaged, and
the artifacts were eliminated for the stimu-
lation period (9). The experiment was
organized in form of no less than two
sessions of stimuli exposure; during each
one the 100 answers were averaged after
the artifacts elimination. The VEP analy-
sis period was 500 ms. The visual VEP in
this case included several waves, among
which three peaks always could be distin-
guished that normally appeared in 75-100
ms and 145 ms. These peaks had negative
(N75), positive (P100), and negative
(N145) polarities.

After the preliminary testing the control
VEP were recorded, while 40 stimuli re-
sponses were averaged. Connected details of
procedure have been described earlier (4).

Deltalycynum («Biopharma», Russia)
was administered intranasal with 2 drops in
the middle part of each nasal meatus
after dissolving of vial portion of delta-lycyn
with 10 drops of distilled water. It should
be noted that one vial contains 0.0003 g of
delta-sleep inducing peptide. That peptide
represents by itself nano-peptide with mo-
lecular weight of 850 D and structured as:
Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu.

The device “Neuro-MS/D”, (“Neuro-
soft” Russia Federation) was used for tran-
cranial magnetic stimulation along with
the appropriate colis and 2.0 Tl inductions
at the height of the magnetic-influence
impulse. The coil was positioned on the
middle line of the occipital zone in the
plane tangential to the cranium surface
according to the adopted cerebellum stimu-
lation technique (3, 4). In the control group
false stimulation was carried out position-
ing the coil perpendicularly to the same
occipital zone (4).

Research results were statistically pro-
cessed applying the ANOVA method and
the Newman-Keuls test.

RESULTS AND DISCUSSION
Dynamics of the development latency
period (LP) P100 revealed that before the
exposure onset in the group of patients with
diabetic retinopathy this index exceeded that
in the control group by 30.0% (p<0.05) (tab.
I). In the first 20 s following the stress peri-
od LP in the group of patients with diabetic
retinopathy exceeded that in the control
group by 33.7% (p<0.05) and was higher
than that before the photo stress exposure by
17.2% (p>0.05). Significant difference from
the control group persisted till the end of the
observation. The amplitude N75-P100 was
by 42.0% (p<0.05) lower in patients with
retinopathy than in practically healthy pa-
tients (p<0.05).

In the first 20 s of post-stress exposure a
53.0% (p<0.05) lowering of the amplitude
N75-P100 was observed in comparison to
the initial background in the group of pa-
tients with retinopathy (p<0.05). Significant
differences in comparison with the control
group have persisted for 60 s of the post-
stress observation. LP and amplitude reco-
vary to the basic value was recorded in the
control group after 73.5+ 3.3 s, and in the
group of patients with retinopathy that peri-
od was longer by 86.7% (p<0.05) (tab. II).

Under conditions of deltalycyn trea-
tment the LP of P100 at the end of 40th s of
post stress period exceeded initial value by
6.5% (p>0.05) (tab. I). The absence of
differences maintained till the end of ob-
servation. The P100 amplitude during first
40 s of post stress period was significantly
less when compared with the initial value
by 20.3% (p<0.05), but at the end of obser-
vation (60th s) the difference was 10.5%
(p>0.05). The total time of recovering of
LP and amplitude of P100 was reduced by
30.7% when compared with patients who
were not treated (p<0.05) (tab. II).
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**TABLE I**

Dynamics of photo stress – provoked worsening of visual evoked potential precipitation in patients with diabetic retinopathy under conditions of deltalycyn and TMS usage (M± SEM)

<table>
<thead>
<tr>
<th>Groups of patients</th>
<th>Investigated index</th>
<th>Before photo stress</th>
<th>Time from the moment of cessation of photo stress (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Control (n=15)</td>
<td>Latency</td>
<td>92.1± 2.2</td>
<td>105.0±3.2#</td>
</tr>
<tr>
<td></td>
<td>Amplitude</td>
<td>9.17± 1.05</td>
<td>6.75±0.80#</td>
</tr>
<tr>
<td>Diabetes retinopathy (n=15)</td>
<td>Latency</td>
<td>119.8± 3.2*</td>
<td>140.4±4.8 *#</td>
</tr>
<tr>
<td></td>
<td>Amplitude</td>
<td>5.32± 0.42*</td>
<td>2.50± 0.23*#</td>
</tr>
<tr>
<td>Diabetes retinopathy + deltalycyn (n=15)</td>
<td>Latency</td>
<td>119.8± 3.2*</td>
<td>127.6± 4.5 *</td>
</tr>
<tr>
<td></td>
<td>Amplitude</td>
<td>5.32± 0.42*</td>
<td>3.12± 0.30*#</td>
</tr>
<tr>
<td>Diabetes retinopathy+ TMS (n=13)</td>
<td>Latency</td>
<td>118.7± 3.4*</td>
<td>130.5± 3.3*#</td>
</tr>
<tr>
<td></td>
<td>Amplitude</td>
<td>5.21±0.35*</td>
<td>3.21± 0.27*#</td>
</tr>
<tr>
<td>Diabetes retinopathy+ eltalycynum+ TMS (n=15)</td>
<td>Latency</td>
<td>119.8± 3.2*</td>
<td>124.3± 3.2*</td>
</tr>
<tr>
<td></td>
<td>Amplitude</td>
<td>5.32± 0.42*</td>
<td>3.93±0.24*#</td>
</tr>
</tbody>
</table>

Notes: *p<0.05 compared with the control group; #p<0.05 compared with the initial data in the same group (ANOVA + Newman-Keuls test).

Exposure to photo stress under the conditions of the preceding TMS application (20 impulses) was accompanied with a tendency of the faster recovering of the P100 LP: in the first 40 s of the post stress exposure the latency exceeded initial value by 8.2% and in 60 s - by 6.4% (p>0.05) (tab. I). The total time of investigated indices recovering was reduced by 19.6% when compared with that one registered in patients without treatment (p<0.05), but it still continued to be 1.5 times longer when compared with the control group (p<0.05) (tab. II).

**TABLE II**

Time of recovery from the photo stress (M± SEM)

<table>
<thead>
<tr>
<th>Investigated index (seconds)</th>
<th>Control (n=15)</th>
<th>Diabetes retinopathy (n=15)</th>
<th>Diabetes retinopathy + deltalycynum (n=15)</th>
<th>Diabetes retinopathy+ TMS (n=13)</th>
<th>Diabetes retinopathy+ eltalycynum+ TMS (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>73.5± 3.3</td>
<td>137.2±11.3*</td>
<td>95.1±6.8*</td>
<td>110.3±12.7*#</td>
<td>82.5± 6.5#</td>
</tr>
</tbody>
</table>

Notes: *p<0.05 compared with the control group; #p<0.05 compared with the initial data in the same group (ANOVA + Newman-Keuls test).
The LP of P100 in patients treated simultaneously with deltalycyn and TMS exceeded the initial value by 3.8\% (p>0.05) at the end of first 20 s of observation (tab. I). Contrary to effects of separate usage of deltalycyn and TMS, combined application of both revealed significant differences of LP when compared to those ones registered in patients with retinopathy without treatment. Thus, at first 20 s such difference was confined to 11.5\%, while at next 20 s – 9.6\% and at the end of observation – 12.2\% (p<0.05). The amplitude of P100 at the end of 40-th s was less by 14.8\% when compared with the initial value (p>0.05). At this moment amplitude exceeded similar index in patients treated only with deltalycyn by 26\% (p<0.05). At 40-th and 60-th seconds of post stressor period amplitude of P100 also exceeded similar index in patients with retinopathy who were given only TMS – by 30,2\% (p<0.05) and 31,2\% (p<0.05) correspondently. The total time of recovery of LP and amplitude in this group was reduced by 39.9\% when compared with the same index registered in patients with retinopathy without treatment (p<0.05) (tab. II).

Thus, the obtained results showed that in patients suffering from the diabetes mellitus with diagnosed retinopathy the following impairments of the VEP characteristics observed: lengthening of the latency period P100 and lowering of the amplitude N75-P100 in comparison to these indices in the control group. Besides, more time (by 86.7\% pertained to control group) it was of need to recover functionally from photo stress.

It may be assumed that the described disorders are the result of a decreased velocity of the nerve impulse conductance along the optic nerve (8). Also quite possible that observed results have been contributed with a selective damage to the ganglion cells and their axons in the central part of the retina as a result of metabolic stress and continuous hyperglycemia. Also it may be assumed that photo stress impairs the ability of the macular photoreceptors to produce the action potential after such stimulation. Meanwhile, a prominent role in the VEP recovery seemingly belongs to the photopigment resynthesis that can be supplied by a sufficient bloodstream volume (4, 7). Hence, the improvement in microcirculation along with the affecting functional state of retinal neurons antidromically from stimulated cerebellar structures might be suspected as main targets for the precipitation of observed positive therapeutic effects. Also it should be noted that both – deltalycyn and cerebellar TMS are able to affect number of neuro-modulator effects including heightening of antioxidative mechanisms (1, 5). The last ones are known as critical for the prevention of diabetic retinopathy (5).

**CONCLUSIONS**

Retinopathy development is linked to prolonged VEP latency period (P100), lowering of the N75-P100 amplitude, as well as to prolongation of the recovery period of the retina’s functional capacity in patients suffering from the diabetes mellitus in the presence of photo stress.

Superlatively administered deltalycyn and cerebellar transcranial magnetic stimulation facilitates a faster recovery of the retina’s functional capacity in response to photo stress in diabetic patients with retinopathy.

Combined usage of deltalycyn and cerebellar transcranial stimulation caused the potentiated shortening of post photo stress recovering of VEP in patients with diabetic retinopathy.
The influence of deltalycyn and transcranial cerebellar stimulation upon recovery of retina after photo stress in patients with diabetic retinopathy

REFERENCES


PREMATURE BIRTH LINKED WITH INFLUENZA COMPLICATIONS IN YOUNG CHILDREN

A group of researchers leaded by Kay Wang, from the University of Oxford in the UK, shows that children younger than two years who were born prematurely are at increased risk of being hospitalized if they develop influenza. One in four children who develop influenza or influenza-like illness will have complications, such as otitis media or pneumonia. The systematic review and meta-analysis, published in Lancet Respiratory Medicine on December 4, analysed 27 studies including more than 14,000 children. In this study, factors that increased the likelihood of hospitalization included neurological disorders (univariable odds ratio, 4.62), prematurity (OR, 4.33), sickle cell disease (OR, 3.46), immunosuppression (OR, 2.39), diabetes (OR, 2.34), and being younger than two years of age (OR, 2.51). When age younger than two was included as a risk factor in a multivariate analysis, children with more than one risk factor had a 74% chance of being admitted to the hospital, while the risk for children with one risk factor was 52% (p<0.0001). These findings provide an evidence-based definition of which children are most at risk of developing complications from influenza. Dr. Wang concluded that interventions aiming to prevent these complications, including vaccination and antiviral medications, should therefore be prioritised in these groups, particularly during seasonal influenza epidemics and influenza pandemics (Anne Harding. Premature Birth Linked With Influenza Complications in Young Children. Medscape. December 14, 2014).