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VESTIBULAR COMPENSATION AFTER UNILATERAL LABYRINTHECTOMY VIA COBRA VENOM COMBINED WITH SOME NEUROTRANSMITTERS

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Abstract

In unilaterally labyrinthectomized (UL) rats a special mathematical analysis of background and evoked extracellular spike activity of Deiters' lateral vestibular nucleus (LVN) single neurons in dynamics of vestibular compensation (VC) at the 4th hour and the 9-35th days of postoperative survival period was carried out. The effects of systemic administration of excitatory (Glutamate - Gl), inhibitory (GABA) and ethanolamine-O-sulphate (EOS) neurotransmitters in the normal, placebo-controlled animals, as well as in those treated with injections of Central Asian cobra venom Naja Naja Oxiana (NOX) (at the 9th, 15th and 35th days after UL+NOX) were tested. In intact animals introduction of GABA led to tetanic (TD) and posttetanic (PTD) depression increasing after its repeated administration. After 9 days, injections of GABA evoked TD with posttetanic potentiation (PTP). At the 15th day, GABA showed no inhibitory effects in the early periods: 4 hours post surgery. At the 15th day EOS caused a TD with posttetanic potentiation (PTP), and then after repeated introduction: a strong depression during the whole poststimulus process. In the same time frame Gl in combination with the EOS gave rise to the TD with PTP. At the 35th day after GABA introduction there was revealed weak restoration of GABA inhibitory effect followed by PTP. By that time, Gl evoked TD with PTP and EOS did not cause TD, but there was only TP with PTD. The protective effect of NOX in these conditions resisting the profound decrease of inhibition, apparently, came to accelerate the VC through early restoration of inhibitory control of neurons on the injured side. This is consistent with a high selective specificity and irreversibility of the effects of snake venoms.

Keywords: unilateral labyrinthectomy; neurons of Deiters' nucleus; the high-frequency stimulation; hypothalamic paraventricular and supraoptic nuclei; snake venom Naja Naja Oxiana (NOX); excitatory and inhibitory neurotransmitters; vestibular compensation.

INTRODUCTION

It is known that vestibular compensation (VC) after peripheral vestibular damage in terms of deprivation of afferent inputs on the example of unilateral labyrinthectomy (UL) is a process of behavioral recovery of visual, motor, and postural reflexes. The biochemical and molecular mechanisms that mediate the VC were not completely studied [*Salzer T. et al., 1994*]. New physiological data on mechanisms of VC after the UL is of interest. In old systems, including vestibular, when restoring the function after injury certain aspects of cellular development and plasticity may be reproduced, in particular, the study of membrane own ("intrinsic") properties of vestibular neurons (VN) of vertebrates [*Straka H. et al., 2005*]. In addition, the vestibular system is favorable for determination of the early steps in the appearance of action potentials and synaptic transmission in the vestibular reflex paths. Their spontaneous synaptic activity during development and recovery of electrical excitability after injury to the peripheral vestibular organs was studied [*Shao M. et al., 2003*]. In turn, the central vestibular neurons play an important role in transformation of multisensory signals of body to motor commands to control visual orienta-

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tion and posture. After the UL on the injured side the activity actually disappears, but after a week it is completely restored [*Ris L. et al., 2003*]. As one of important factors in the recovery of spontaneous pacemaker activity on the injured side, almost 3-fold increase in low-threshold calcium current was discovered [*Ris L. et al., 2003*]. Furthermore, during the VC membrane properties and discharge patterns of "tonic" (Type A) and "kinetic" (type B) neurons with low- and high-frequency dynamics of the responses, respectively undergo a short and long-term plastic changes that contribute to the maintenance of their level of activity and excitability [*Straka H. et al., 2005*]. It should be noted that the background activity in normal and viral load after the UL on the injured side, has several unique features and in many ways is still poorly understood [*Straka H. et al., 2005*]. Data on existence of inhibitory vestibular internuclear connections is well known. The study of spiking-behavioral neurons of the intact side in guinea pigs at the first hour, the first and second days or a week after the UL [*Ris L., Godaux E., 2004*], as well as after bilateral labyrinthectomy, showed a return to the norm within a week [*Ris L., Godaux E., 2004*]. The asymmetry of lack of stimulating effects from the damaged labyrinth and the persistent inhibitory effect on intact side, as the driving force for the recovery of activity is discussed. A two-three times more powerful ipsilateral excitatory than the contralateral inhibitory effects were obtained [*Ris L., Godaux E., 2004*]. The fact that vestibular neurons characterized by constant tonic activity cease to be discharged after the UL and in a week reduce the discharge rate up to the initial level allowed suggesting that it is realized through the transformation of synaptic currents in samples of spike discharges [*Guilding C., Dutia M., 2005*].

Finally, the neurochemical study of molecular mechanisms of neural and synaptic plasticity in vestibular neurons, involved in the VC after the UL revealed that its development reduced the imbalance in releases levels of various amino acids (aspartate, glutamate, glutamine, glycine, taurine, alanine), except glutamine [*Yu H. et al., 2006*]. In addition, the bilateral imbalance of glutamate release leading to nystagmus is gradually decreased, being accompanied by a reduction in their frequency [*Yu H. et al., 2006*]. Such internuclear re-balance of excitability [*Inoue S. et al., 2003*], including the synthesis of polyamines stimulated by UL, speeds up the VC, which provides for development of new therapeutic strategies for treatment of vestibular disorders [*Kim H. et al., 1997*].

In this paper we present a comparative analysis on significance of inhibitory and excitatory neurotransmitters in the norm, during UL and the protective effect of the central Asian cobra venom NOX (Naja Naja Oxiana) in the aspect of contribution to inhibition in dynamics of VC at the 4th hour and at 9-35 days after the UL in the placebo control and treated animals. Previously we studied in detail the effect of systemic administration of melanin and GABA (separately and combined) on single neurons of substantia nigra and spinal cord motoneurons [*Kamalyan R. et al., 2007; Sarkissian J., 2007*], as well as published results on effects of NOX in the dynamics of VC during UL [*Galoyan A., 2010*].

MATERIAL AND METHODS

Experiments were carried out in normal and UL animals (adult male Albino rats; body weight: 230±30 g) without (sham control) and with NOX administration (5% LD50, 1 mg/kg, i/m three days after UL).

In electrophysiological studies extracellular recording of Deiters' lateral vestibular nucleus (LVN) single neurons spike activity to high-frequency stimulation (HFS) of paraventricular (PV) and supraoptic (SO) nuclei of hypothalamus in the following series of acute experiments were performed: 1) in norm, 2) at the 4th hour and the 9-35th days after the UL on injured side in placebo-controlled animals, and 3) animals treated with NOX injections to identify the dynamics of the effects of intramuscular injections of GABA, EOS, glutamate (isolated and combined at doses of 1 mg/kg and 2 *mg/kg*).

During the acute experiments animals were immobilized by 1% dithylinum (25 *mg/kg, i/p*) and under artificial ventilation the section of spinal cord at T1-T3 level) was carried out with ultrasound scalpel to achieve encephale isole preparation. All the procedures utilizing rats

were performed according to the "principles of laboratory animal care" (NIH publication No. 85-23 revised in 1985), as well as the specific rules provided by the animal care and use committee of the national medical and health service. In stereotaxic apparatus the trepanation of the skull was realized from bregma till lambda and dura mater was removed. Stereotaxic orientated glass electrodes of 1-2 μM diameter tip were filled with 2M NaCl and inserted into LVN for bilateral recording of single neurons spikes flow activity evoked by bilateral high frequency stimulation (HFS) of PV and SO hypothalamic nuclei (rectangle current pulses: 0.05 *ms*, 0.12-0.18 *mV*, 0.32 *mA* and frequency of 100 Hz during 1s). Stimulating and recording electrodes were inserted according to stereotaxic coordinates of the rat atlas [Paxinos G., Watson C., 2005]: supraoptic nucleus (SON): anteroposterior (AP): 1.3, lateral (L): ±1.8, dorsoventral (DV): + 9.4 *mm*; paraventricular nucleus (PVN): AP: 1.8, L±0.6, DV+7.8 *mm*; lateral vestibular nucleus (LVN): AP: 11.5, L±2.5, DV+7.0 *mm*. Post stimulus activity was revealed as tetanic potentiation (TP) and depression (TD) followed with posttetanic potentiation (PTP) and depression (PTD) of different latency, intensity, and duration. On-line registration was realized on the basis of program providing selection of the spikes by means of amplitude discrimination. After selection, the pulse flow was analyzed by means of a special mathematical program before and after stimulation for getting "raster" of single neurons pre- and post stimulus spike flows in real time. There are also shown histograms of the sum and averaged frequency, histograms of the spikes presented in raster, peri-event time histograms (PETH), as well as Cumulative and Frequency histograms. For selected comparable groups of neuronal spiking the similar complex averaged PETH (PETH Average), cumulative (Cumulative Average) and frequency (Frequency Average) histograms were constructed. On average, during each record up to 10-15 post stimulus trials were carried out. This special mathematical program (developer: V.S. Kamenetski) allows separating stimuli, superposed on action potential during their close succession in the process of TP and TD and avoiding traditional complex intracellular recording approach of long-term tetanic potentiation and depression. This allows taking into consideration strictly permanent tetanic effects in comparison with less stable posttetanic ones too. To determine the statistical significance of differences in duration of interspike intervals before and after the stimulus we used nonparametric criterion for testing homogeneity of two independent samples - Two Sample Wilcoxon-Mann-Whitney' criterion (Wilcoxon-Mann-Whitney test). Since the number of recorded spikes was large enough (up to several hundreds of spikes in 10-second interval after the stimulus), the variety of this test was used, taking into account its asymptotic normality: z-test. Comparison of critical values with the tabulated values of the normal distribution at a significance level of 0.05, 0.01 and 0.001 (for different trials) shows that as a result of HFS for most samples of neuronal activity spiking there is a statistically significant change with a minimum significance level of 0.05

RESULTS

The plastic reorganization of Deiters' nucleus neurons in the dynamics of changes after UL, HFS of hypothalamic nuclei, systemic injection of GABA, Gl, EOS and use of snake venom NOX as a protector was studied in rats.

In intact animals GABA suppressed all pre- and poststimulus activity of LVN neurons evoked by HFS of hypothalamic PVN and SON (Figure 1A and D, respectively) at 64-66 *min* (see MBE, MTT и MPE) with more pronounced TD and TP+PTD sequence during repeated injections of GABA already at 25-27 *min* (Figures 1 B, E; 7 A). The effect of systemic administration of NOX (5% of the LD50) in intact animals (Figure 1 C, F) was limited to the initial TD with early PTD and late PTP (Figure 1C n01, n02 and 1F n01-n03) followed by TD and early PTP+PTD (Figure 1C n03, n04 and 1F n04-06). All the mentioned can be seen on this Figure and on the rest of Figures as well. Four hours after the UL HFS of PVN and SON and injections of GABA (1 *mg/kg*) evoked TD in LVN neurons of the injured side with farther stabilization of activity (Figures 2 A; C, n1-11; 7 B). In case of repeated administration of GABA (2

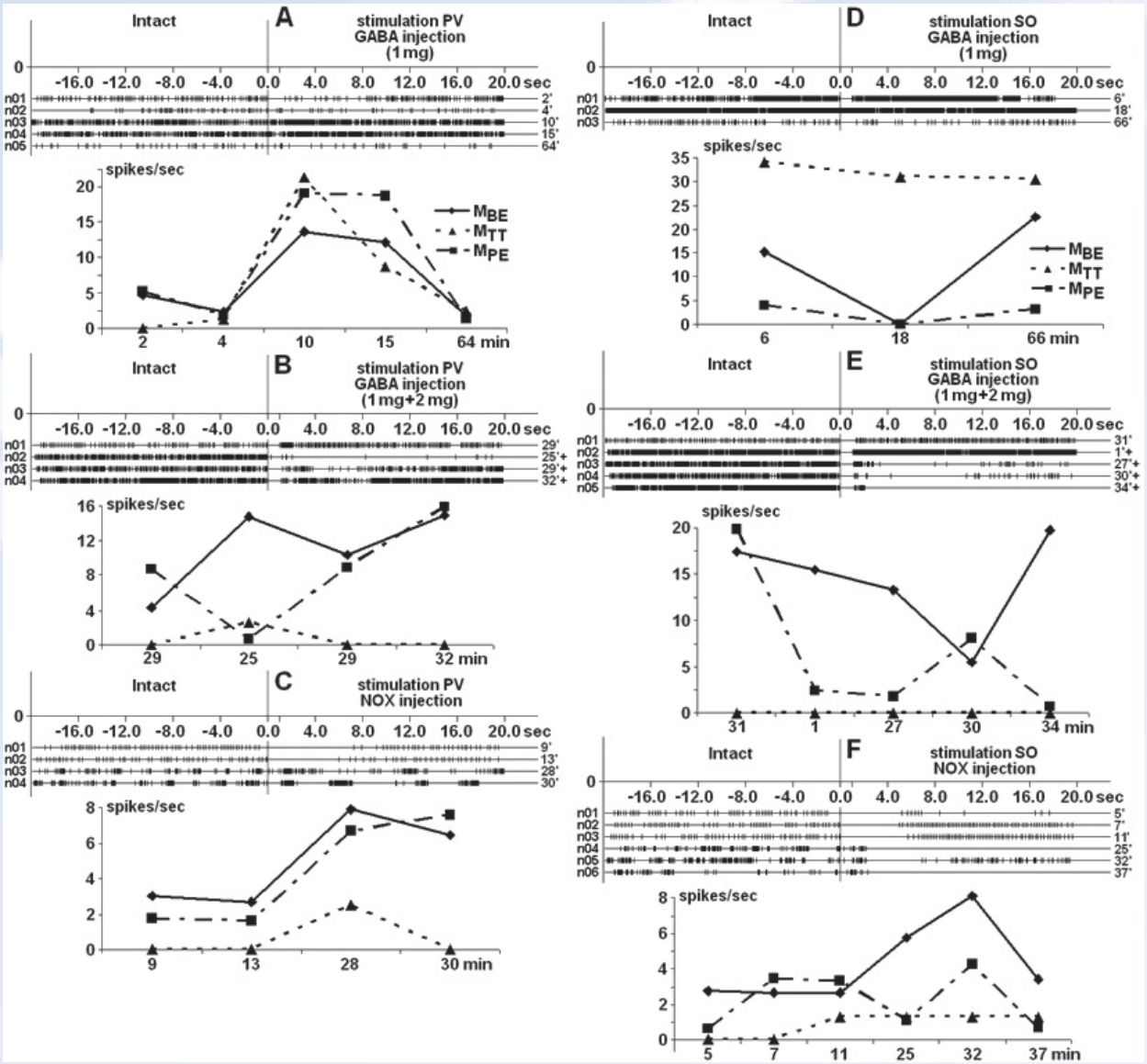

Figure 1. *A-F - "raster " of the pre- and poststimulus mixed TD+PTP (A, B) and depressor TD+PTD (C-F) displays of spike activity in real time 20 seconds (before and after stimulation) of 3 LVN single neurons (A, D; B, E and C, F) in norm with systemic administration of GABA and NOX (C, F) to HFS of PVN (A-C) and SON (D-F). Here and in other Figures: from the bottom of the diagram the dynamics of changes of the average (M) for time periods prior to stimulation (BE - before event), at the time of tetanization (TT - tetanization time) and after stimulation (PE: post event); left of the raster: number of trials (n), right: injection time of neurotransmitter in minutes (+: re-injection, 0': baseline). The rest of notations are in the Figure.*

mg/kg) intensification of inhibition both before and after the HFS of PVN and SON with TD and the prolonged PTD (Figure 2 A; C, n12-14 and n12-16, respectively), are presented on the diagram. In 9 days after the UL + NOX, injection of GABA during HFS of PVN (Figures 2; 7 C) and SON (Figures 2 D; 7 C) initiated the TD with PTP, including cases with repeated administration of GABA. At the 15th day after the UL + NOX on HFS of PVN, GABA led to the formation of TP accompanied by early PTP and subsequent PTD (Figure 3 A) or TD with PTP (Figures 4 C; 7 D). By that time, EOS evoked TD (Figures 3 B; 4 A) or TD with PTP (Figure 4 D), while under repeated administration (after 30 min) more pronounced TD with a strong PTP (Figure 3 B) was recorded. At the 15th day and HFS of SON, GABA induced TP with early PTD or PTP (Figures 3 D; 4 G; 7D), and upon injection of EOS: TD with early-PTP (Figures 3 E; 4

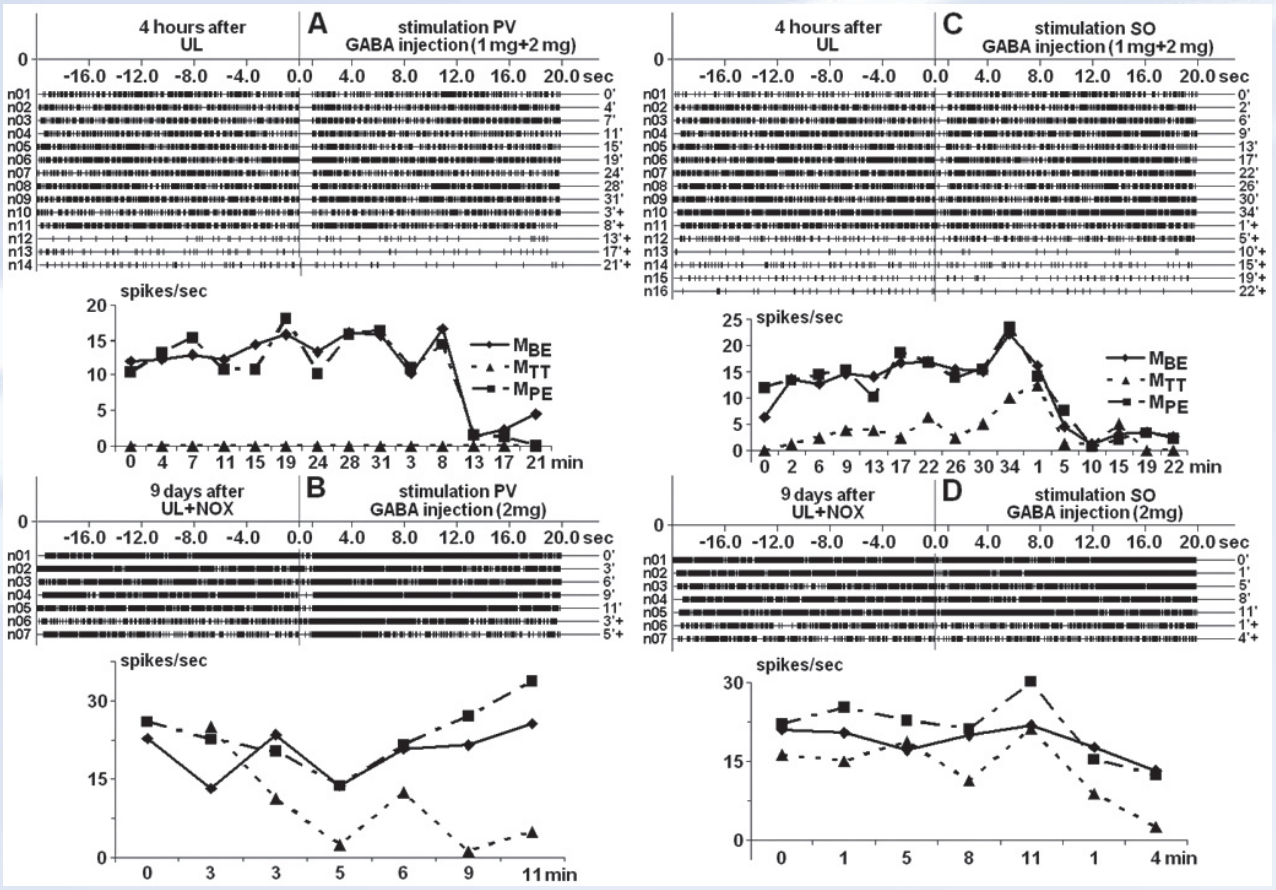

Figure 2. A-D - «raster « of the pre- and poststimulus depressor TD+PTP (A-D) displays of spike activity of 2 LVN single neurons (A, C and B, D) 4 hours (A, C) and 9 days (B, D) after UL with systemic injection of GABA and NOX to HFS of PVN (A, B) and SON (C, D). The rest of notations are in the Figure.

H) or TP (Figure 4 E), and after its repeated injections: TD with prolonged PTD (Figure 3 E). At the same time frame, on the background of Gl administration of EOS during HFS of PVN led to the early PTP or TD with PTP (Figures 3 C; 4 B; 7 E), whereas under HFS of SON the excitatory effect of Gl was not manifested at all and TD with PTD (Figure 3 F) or with PTP (Figures 4 F; 7 E) was recorded. At the 35th day after the UL + NOX, injection of Gl with HFS of PVN was accompanied by the display of TD with PTP (Figure 5 C), and under SON — TP with PTP (Figure 5 F); however, often both in response to PVN and SON evoked exclusively inhibitory TD with PTD effects (Figures 6 A, B; 7 G). By this time the HFS of PVN with EOS evoked TD with PTD (Figures 5 A; 7 G), while injections of GABA caused a weak TD with early PTP (Figures 5 B; 7 F), whereas to HFS of SON predominantly PTP (Figures 5 E; 7 F) was evoked. As to the use of GL + EOS, at this time TD+PTD and TD + early PTD were recorded both to PVN and SON stimulation (Figures 6 C, D; 7 H). Finally, all the above mentioned is shown in Figure 7 as PETH Average and Frequency Average histograms to HFS of PVN and SON for the cases of Intact + GABA (A), 4 hours after UL + GABA (B), 9 days after UL+NOX + GABA (C), 15 days after UL+NOX + GABA (D), 15 days after UL+NOX+Gl+EOS (E), 35 days after UL+NOX+GABA (F), 35 days after UL+NOX+Gl (G, Groups A, B), UL+NOX+EOS (G, Groups C, D) and 35 days after UL+NOX+Gl+EOS (H). It is of interest that on the 9th day after UL+NOX, under the action of GABA, in fact on average, the test found no significant difference in the effects evoked by both the PVN and SON.

DISCUSSION

Results of this study showed that at a later period after the UL+NOX (15 days) actually GABA did not show its typical inhibitory effect detected in the early postoperative period

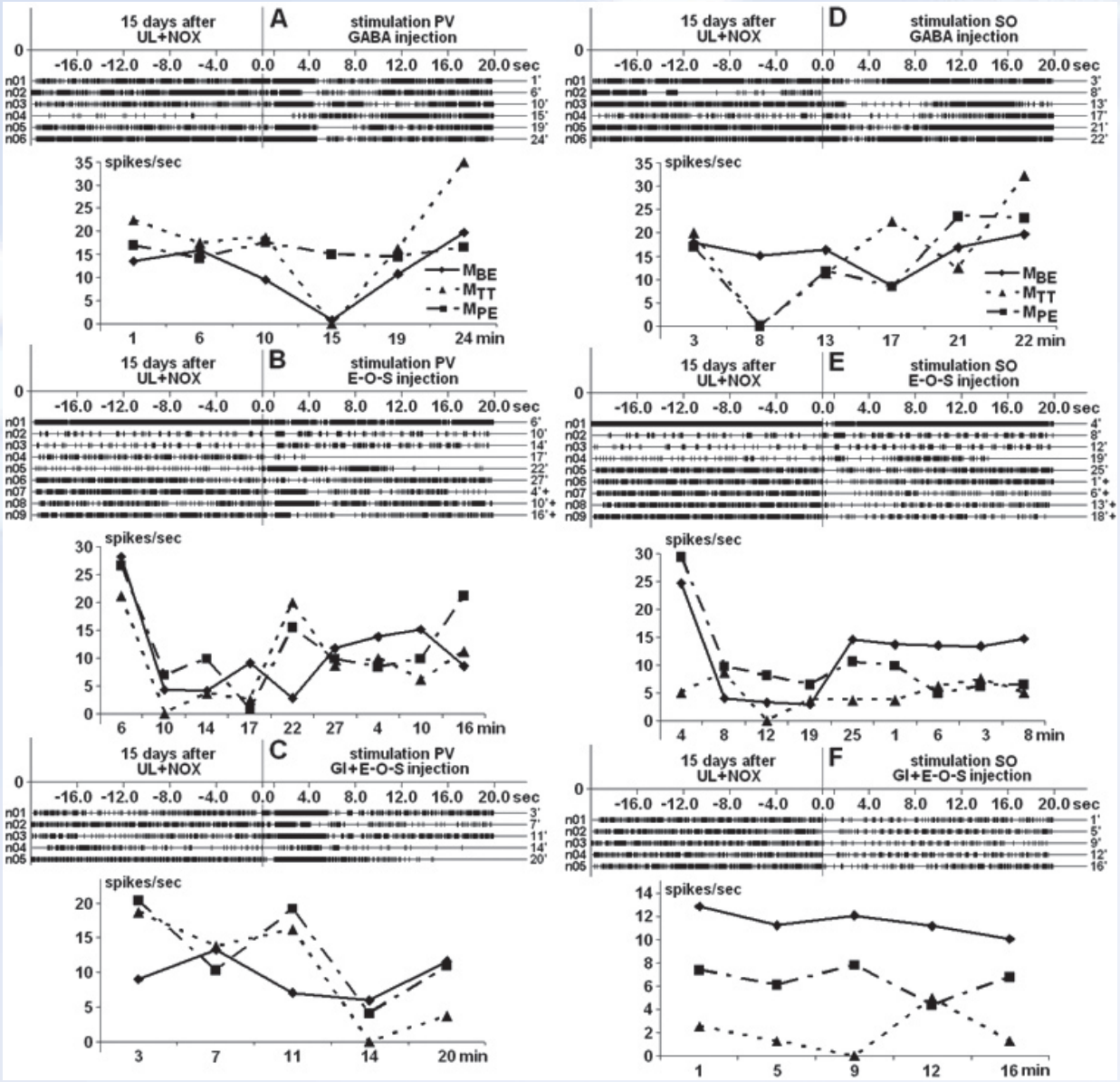

Figure 3. *A-F - «raster « of the pre- and poststimulus excitatory TP+PTP (A,D), inhibitory TD+PTD and mixed (B, C, E and F) displays of spike activity of LVN single neuron at the 15th day after UL+NOX with systemic injection of GABA (A, D), EOS (B, E) and Gl+EOS (C, F) to HFS of PVN (A-C) and SON (D-F). To the left of peristimulus histograms: the number of trials (n); right: injection time of neurotransmitter in minutes. The rest of notations are in the Figure.*

(4 hours). At the 15th day EOS, apparently due to promotion of GABA accumulation caused a TD with PTP, while its re-introduction evoked a powerful depression for all the period of post-stimulus display of activity. Gl at the 15th day caused a TD with PTP, but on the background of EOS and PVN stimulation only early PTP was observed. At the 35th day, EOS no longer evoked TD and there was only TD with PTD. However, a weak recovery of the inhibitory effect of GABA followed by PTP was revealed. Gl to this term gave rise to TD with PTP, while EOS did not cause TD and there was only TP with PTD. As for the intact animals, the introduction of GABA gave rise to TD with PTD, which were more powerful after re-introduction.

Explanation of the results can be obtained by reviewing the recent literature data on UL. It should be noted that the main reason of oculomotor and postural symptoms of unilateral vestibular deficiency is misbalanced commissural inhibitory system and that its re-balance occurs in parallel with behavioral recovery during VC [*Bergquist F. et al., 2008*]. After the UL, increase of excitability in vestibular neurons on the injured side may be the result of

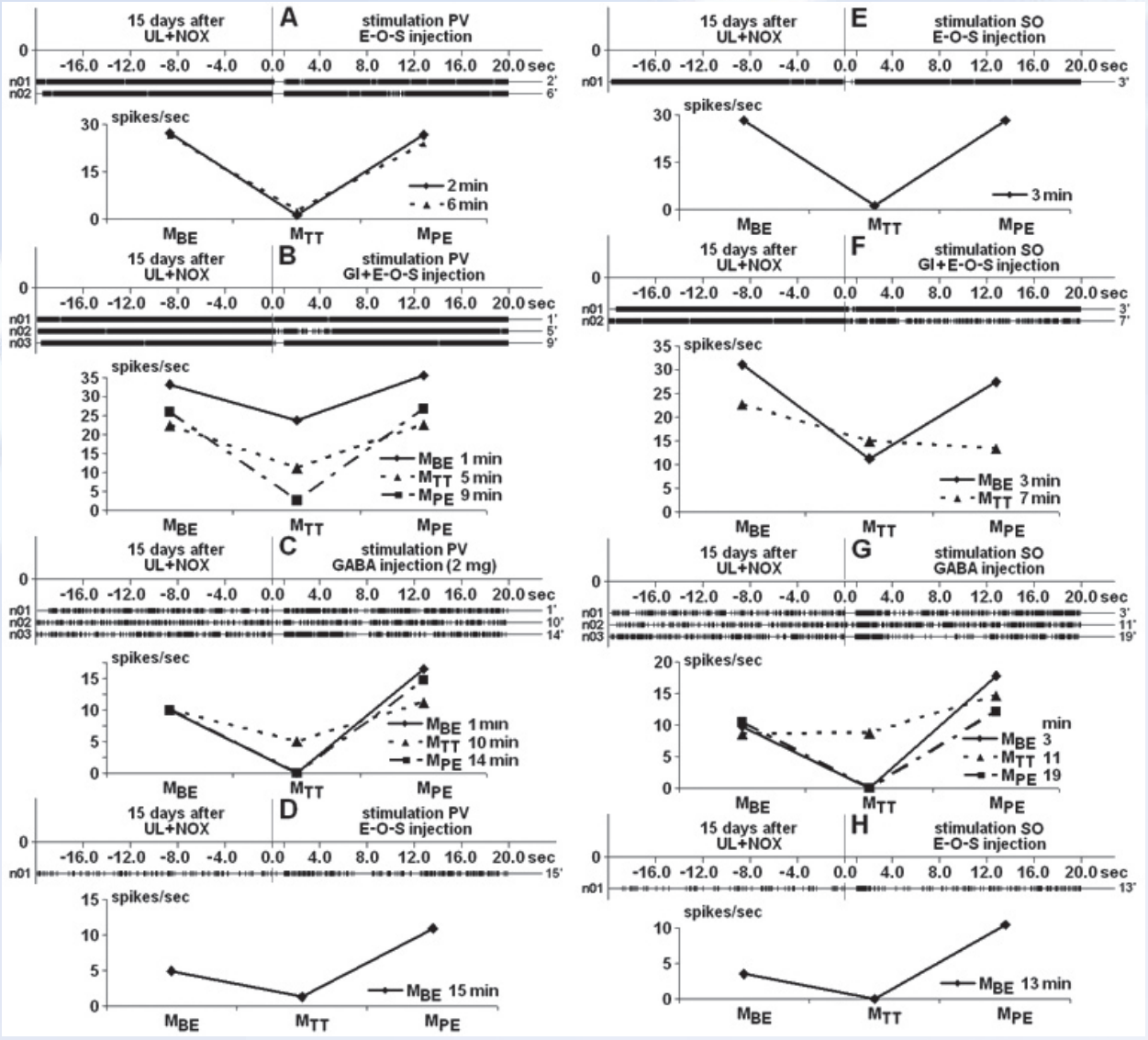

Figure 4. *A-H – «raster « of the pre- and poststimulus inhibitory TD, TD+PTD and mixed TD+PTP (C, D, G, H) displays of spike activity of 2 LVN single neurons (A, B, E, F and C, D, G, H) at the 15th day after UL+NOX with systemic injection of EOS (A, D, E and H), Gl+EOS (B, F) and GABA (C, G), and to HFS of PVN (A-D) and SON (E-H). The rest of notations are in the Figure.*

GABA receptors down-regulation opposing the excessive commissural inhibition. It is assumed that restoration of pacemaker resting discharge in deafferented neurons is responsible for increased pacemaker excitability [*Cameron S., Dutia M., 1997*]. In addition, the lack of excitatory inputs on the injured side causes a decrease in their sensitivity to inhibitory amino acids, which should facilitate the restoration of normal bilateral balance of averaged resting discharge of vestibular neuron [*Vibert N. et al., 2000*]. In other words, there is a down-regulation of the effectiveness of GABA (B) receptors on the ipsilateral side and up-regulation - on the contralateral one [*Magnusson A. et al., 2000*]. It is also believed that the adaptive regulation of GABA receptors efficiency in vestibular neurons may be an important mechanism of cellular homeostasis or bilateral balance of their excitability [*Yamanaka T. et al., 2000*]. In fact, long-term down-regulation of slow GABA (B) receptors on the affected side may be a factor counteracting long-term decrease of excitatory input in deafferented neurons [*Johnston A. et al., 2001*]. The presence of proper mechanisms to increase the excitability immediately after deafferentation and changes in the effectiveness of synaptic inputs in later period is proved. This is evidenced by the absence of early synaptic blockade (after 4 hours), whereas later

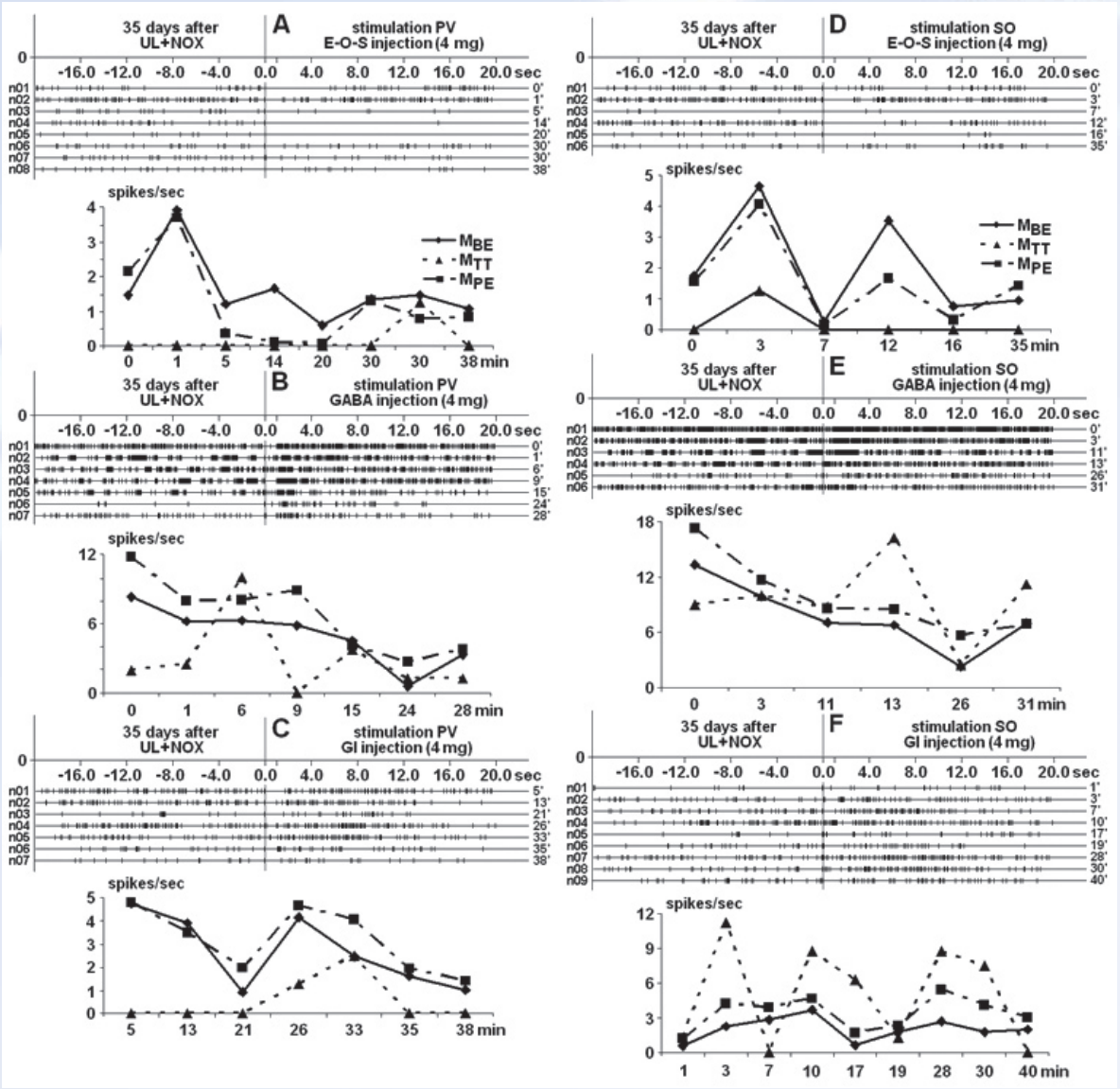

Figure 5. *A-F - «raster « of the pre- and poststimulus inhibitory TD+PTD, excitatory (E, F) and mixed TD+PTP (B, C) displays of spike activity of 2 LVN single neurons (A, D and B, C, E, F) at the 35th day after UL+NOX with systemic injection of EOS (A, D.), GABA (B, E) and Gl (C, F) to HFS of PVN (A-C) and SON (D-F). The rest of notations are in the Figure.*

(after 48 hours, 1 week) blockade rearranged the activity to norm [*Guilding C., Dutia M., 2005*]. It was also shown that immediately after the UL there is a significant increase in the release of GABA on the injured side, which is not prevented by bilateral flocculectomy indicating that the effect is liable to depend on hyperactivity of commissural inhibitory neurons. With the improvement of behavioral symptoms (more than 96 hours) GABA levels on the injured side approached to the norm, while those on the intact side were not significantly changed at the early stages of the VC, but dropped in the later period (96 hours) [*Paxinos G., Watson C., 2005*]. Moreover, it was shown that at the early stage of VC high density of GABA (A) and GABA (B) receptors may not be involved in the restoration of a normal resting discharge of deafferented vestibular neurons [*Eleore L. et al., 2005*]. Finally, we showed that on the injured side the long-term depression decreased and long-term potentiation intensified depending on the activation of NMDA receptor, which increases the synaptic efficacy. The converse effect due to the activation of GABA neurons occurred on the intact side. These changes in synaptic plasticity may contribute to bilateral re-balance of tonic discharge during the VC,

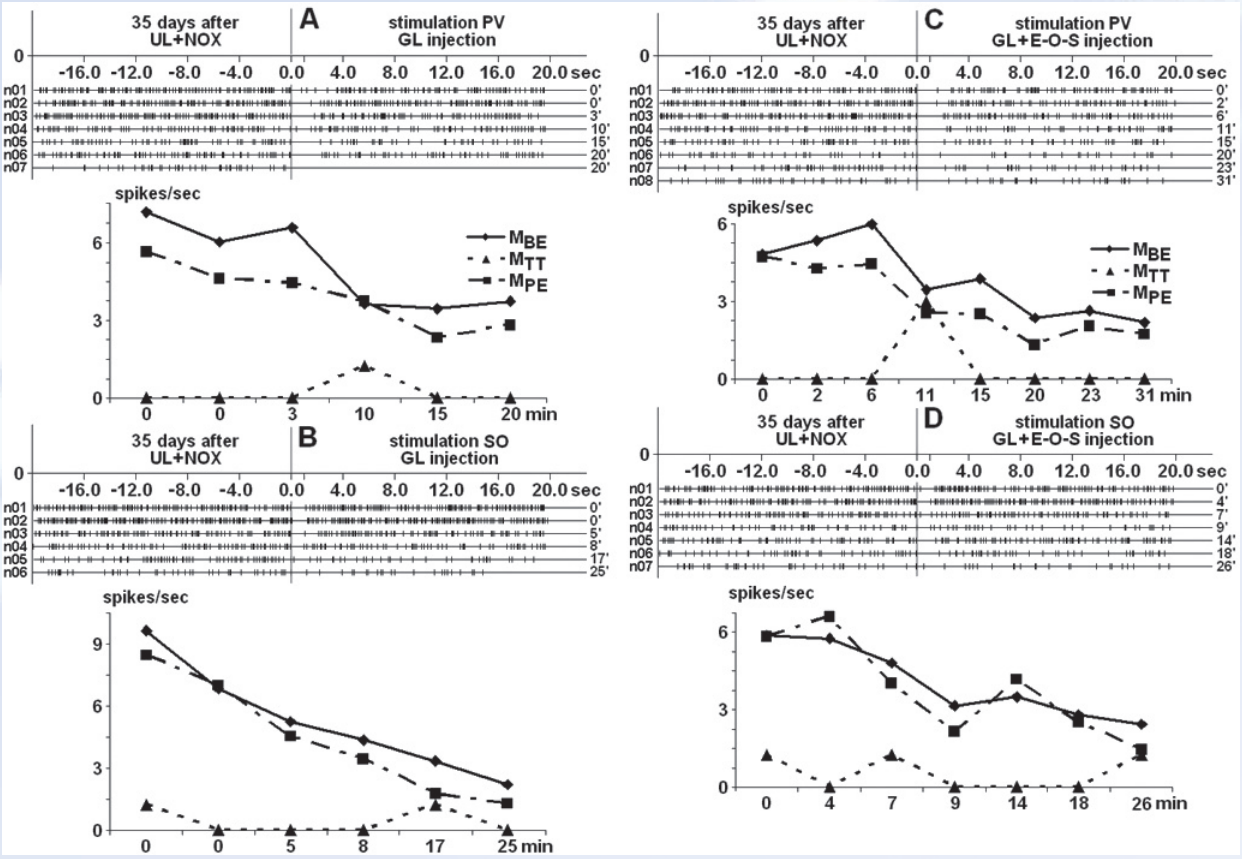

Figure 6. *A -D - "raster" of the pre- and poststimulus inhibitory (TD+PTD) displays of spike activity of 2 LVN single neurons (A, B and C, D, respectively) at the 35th day after UL+NOX with systemic injection of Gl to HFS of PVN (A, C) and SON (D, F). The rest of notations are in the Figure.*

as well as increased responses of deafferented neurons [*Pettorossi V. et al., 2003*]. Mentioned literature data were obtained in the absence of pharmacological intervention, while our studies were performed under the protective action of NOX venom. The protective effect of NOX restoring in these conditions the profound decrease in inhibition, apparently, came down to acceleration of VC through early restoration of inhibitory control of neurons on the injured side. This is consistent with high specificity and irreversibility of effects causing the long-term action of snake venoms [*Bowman W., Sutherland G., 1986; Cook N., 1990*]. In addition, based on dendrotoxins of the family of Elapidae, to which the NOX also belongs, there were synthesized compounds selectively blocking some subtypes of voltage-dependent K+ channels (fast activated) in neurons, through which their excitability is controlled [*Rudy B., 1988; Cook N., 1990*].

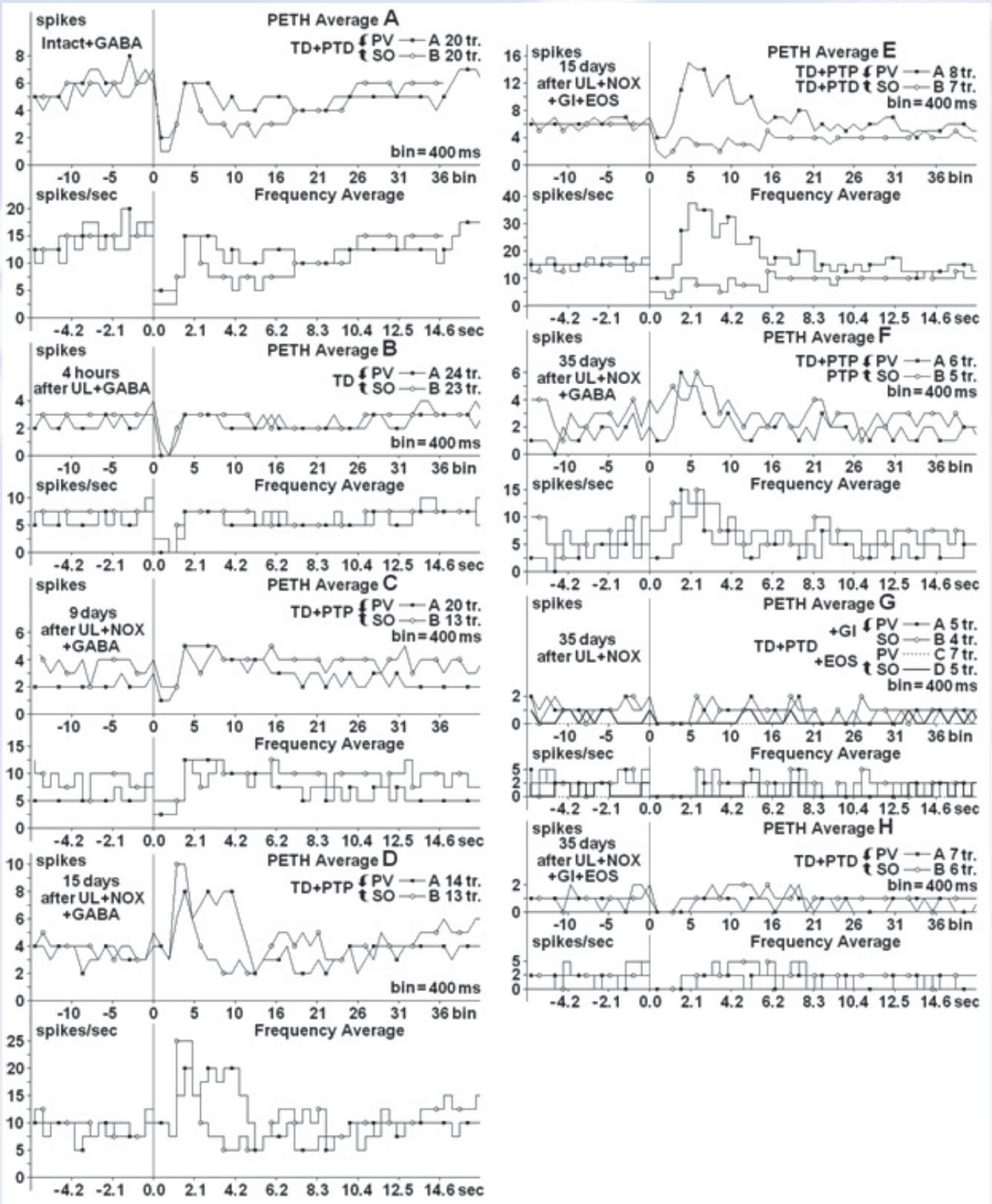

Figure 7. *PETH Average and Frequency Average histograms of LVN neurons activity in response to HFS (100 Hz, 1 sec) of PVN and SON are presented in proportions of depressive and excitatory poststimulus manifestations in an intact animal (A), in conditions of UL after 4 hours (B), UL coupled with NOX after 9, 15, and 35 days with use of GABA (B-D, F), after 15, 35 days with use of Gl+EOS (E, H) and after 35 days with use of GL and EOS separately (G). The rest of notations are in the Figure.*

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METABOLIC SYNDROME, DIETARY INTAKE, AND FOOD HABITS IN PATIENTS WITH AND WITHOUT CORONARY HEART DISEASES: FIRST COMMUNICATION

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Abstract

Heart diseases and stroke cause most deaths in the developed world. There are several age, sex, and race related regularities in mortality from cardiovascular diseases (CVD). The continuing rise in prevalence of obesity and metabolic syndrome (MS) in many countries constitutes a serious threat to public health, increasing mortality, disability, and health care costs. The dietary habits create serious health concerns, including obesity, hypertension, diabetes, cardiovascular diseases, and even some types of cancer.

The aim of this study is to determine the relationship between MS, dietary intake, and food habits in patients with and without coronary heart diseases in Yerevan Health Care Centers.

The present study is conducted among patients of the Yerevan State Medical University hospitals and polyclinics. Usual dietary intake is assessed with the use of a semi-quantitative Food Frequency Questionnaire (FFQ). Serum chemistry values are determined at the hospital laboratories. Food habits and life style information are collected using a general questionnaire; anthropometric indices and blood pressure are measured by appropriate methods. Data collected from totally 640 patients is subject to be analyzed using appropriate parametric and non-parametric tests. Modern software for statistical analyses are used (SPSS, Epi Info 2000, etc.).

The present communication is the first to reflect our study; the most important outcomes will contribute to health policy making in the public awareness programs on preventive measures of MS and CVD in Armenia.

Keywords: Coronary heart disease, metabolic syndrome, dietary intake, Food-Frequency Questionnaire.

INTRODUCTION

Diseases of heart and the stroke cause most deaths in the developed world. Mortality from all heart diseases increases with age in all races in the USA. There are several age, sex, and race related regularities. Until the age of 65 years, black men have the highest rates of coronary heart disease (CHD) deaths; thereafter white men have the highest rates. Black women have higher rates than white females at all ages [*Mahan K., Escott-Stump S., 2008*]. Each year 600,000 Americans have a stroke, and 159,000 die of stroke. Strokes account for 17% of cardiovascular disease (CVD), and rates of death are 35% higher in blacks than in whites [*Linda K., 2001*]. Persons with the metabolic syndrome (MS) are at a greater risk of CVD [*Azadbakht L. et al., 2005; Esposito K. et al., 2007*]. The continuing rise in prevalence of obesity and MS in the USA constitutes a serious threat to public health, increasing mortality, disability, and health care costs [*May A. et al., 2008*].

As recommended by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) "metabolic syndrome" is defined as the presence of three or more of the following components [*Mahan K., Escott-Stump S., 2008*]:

1. abdominal adiposity (waist circumference > 88 *cm*);
2. low serum HDL cholesterol < 40 *mg/dL* (1.03 *mmol/L*) in men and <50 *mg/dL* (1.3 *mmol/L*) in women;
3. high serum triacylglycerol (≥150 *mg/dL*);
4. elevated blood pressure ≥130 (systolic)/ ≥85 (diastolic) *mm Hg*; and
5. abnormal glucose homeostasis (fasting plasma glucose≥100 *mg/dL*).

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