THE NEW ARMENIAN
MEDICAL JOURNAL
Vol. 3 (2009), N 1, 29 - 43

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HYPOTHALAMIC CONTROL OF THE ACTIVITY OF DEITERS' NUCLEUS NEURONS

L.E. Hambardzumyan[1], L.P. Manukyan[1], V.A. Chavushyan[1], I.B. Meliksetyan[1], S.A. Badalyan[1], N. Khalaji[3], A.L. Hovhannisyan[1], L. Simon[2], V.A. Sarkisian [1], J.S. Sarkissian* [1]

[1] - L. Orbeli Institute of Physiology, National Academy of Sciences of Yerevan, Armenia,
[2] - Laboratory of Sensorimotor Adaptation, Department of Anatomy, Histology and Embryology, I.F. Semmelweis University Medical School, Budapest, Hungary
[3]Urmia University of Medical Sciences, Department of Hospital Emam, Urmia, Iran.

Abstract

The excitatory and inhibitory tetanic and post-tetanic changes of lateral vestibular nucleus (LVN) of Deiters' single neurons pulse flow frequency activity evoked by high frequency stimulation of hypothalamic Paraventricular (PVN) and Supraoptic (SON) nuclei was revealed. Depressor effects might be assumed of both true inhibitory and/or disfacilitatory origin. Producing depression from the brain higher endocrine centers is important for prevention of possible intensification of vestibular tonus alongside with exclusion of flexor-extensor balance, which is controlled by motor centers of the brain. The existence of excitatory reaction indicates to delicate regulatory action of PVN and SON to LVN as well. By means of Ca^{2+}-dependent acidic phosphate method there were shown big polygonal LVN neurons, with dichotomized distant branching from the cell body and high activity of enzymes in dendrites and around the nucleus. By horseradish peroxydase (HRP) transport method the retrograde labeled large cells were shown in the medial and ventral parts of SON. Projecting to LVN small labeled source-cells unlike the large cells were predominantly revealed in dorsal and medial divisions of PVN.There were also found transient and anterograde marked preterminals The direct bilateral connections of LVN with PVN and SON indicate that LVN acts not only as an integrative structure, coordinating and controlling different motor actions concerned with regulation of posture and orientation in space, but is also involved in the processes of central regulation on autonomic functions.

Keywords: single neuronal activity; lateral vestibular nucleus (LVN) of Deiters'; tetanic stimulation; paraventricular nucleus of hypothalamus (PVN); supraoptic nucleus of hypothalamus (SON)

Introduction

Neurons of the vestibular complex realizing perception and analysis of information on position and displacement of the body in space transform it to motor commands for the control of posture. Over the last years in a number of vertebrates the relations of intrinsic membrane properties of medial vestibular nucleus (MVN) neurons to their response patterns, discharge dynamics and computational abilities were intensively studied by means of *in vivo* and *in vitro* experiments. During *in vitro* studies among MVN neurons the two large subgroups (A and B) were distinguished, which differ in spike pattern and after hyperpolarization, reflecting the differences in their K^+ conductivity. Low ("tonic") and high ("kinetic") frequency neurons were attributed to A and B types, respectively. Therewith, membrane properties and pattern of discharges of these neurons in postnatal period developed through expression of conductivity of ion channels concerned [*Straka H. et al., 2005*]. In its turn, the

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Address for correspondence:
22 Orbeli Bros Street,
L. Orbeli Institute of Physiology, NAS (Armenia)
0028 Yerevan, Armenia
E-mail: vsargsyan@neuroscience.am

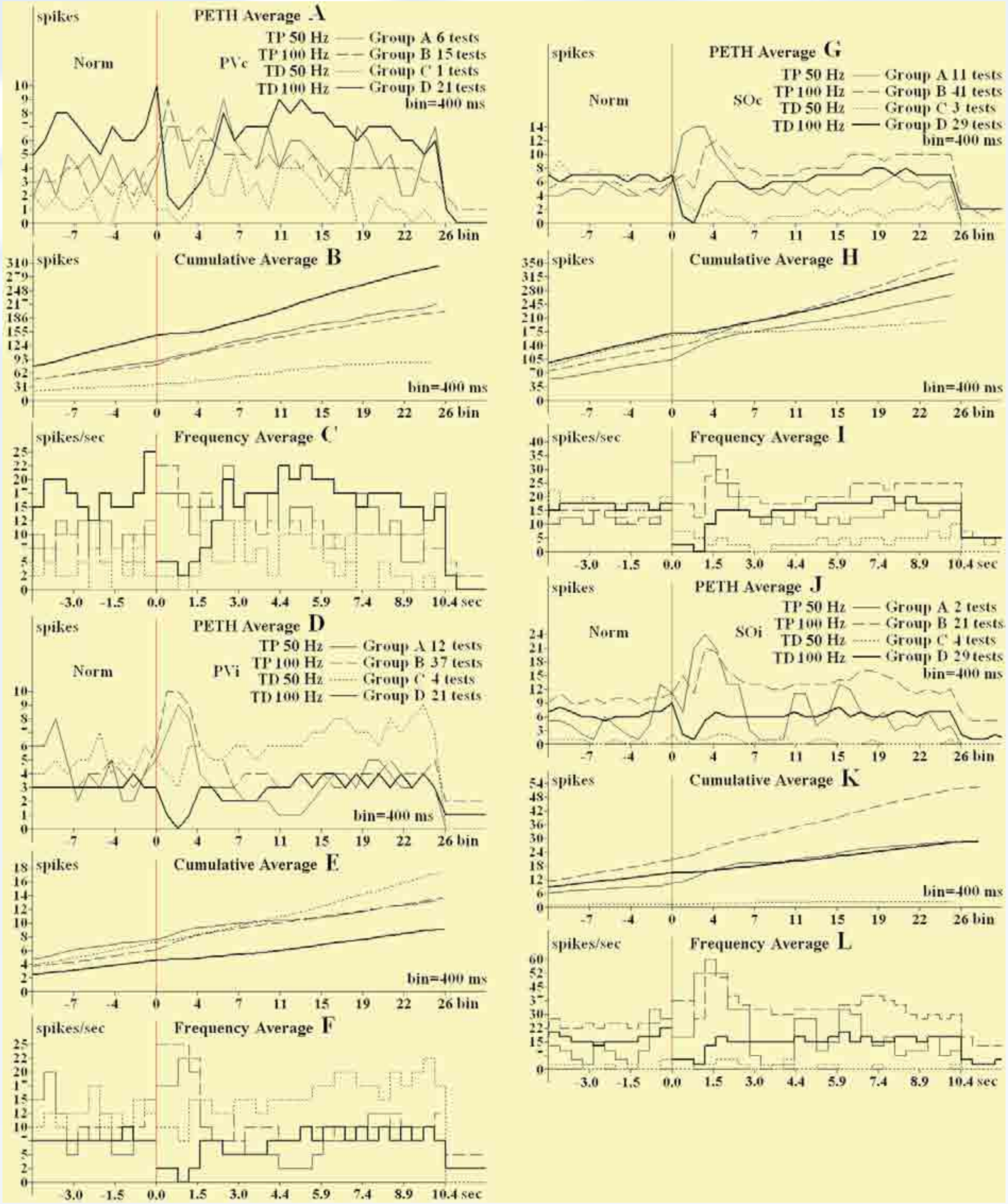

Figure 1. *A - G – Complex average (PETH Average), cumulative (Cumulative Average) histograms and frequency histograms (Frequency Average) of LVN neurons activity spiking to stimulation PVN (PV$_c$ – A- C; PV$_i$ –D-F) and SON (SOc – G-I; SOi – J-L) for excitatory (Group A and B; tetanic potentiation-TP) and inhibitory (Group C and D; tetanic depression-TD) effects at frequency of 50 Hz (Group A-C) and 100 Hz (Group B-D) during 1 sec. Next to each Group the number of trials (tr.) is given. For A, B, D, E, G, H and K, L, bin=400 ms.*

vestibular system due to synaptic capacity and plasticity can be used as an attractive model to understand the influence of changes in cellular and synaptic activity for learning and memory in behavior yielding to quantitative determination. Mechanistic analysis of the burst potentiation pattern in the neurons of vestibular nuclei disclosed new norms of plasticity, applicable to spontaneously bursting neurons in the other regions of the brain [*Gittis A., du Lac S., 2006*]. Moreover, the vestibular system is favorable for testing early steps in origination of synaptic transmission between neurons of vestibular reflex paths, the spontaneous synaptic activity of which was studied in the period of development [*Shao M. et al., 2006*].

Vestibulospinal neurons of the lateral vestibular nucleus (LVN) of Deiters' cells represent as a basic upper segmental center of regulation of the posture and locomotion. Recently the interrelations of LVN with numerous brain structures relating the regulation of posture, equilibrium, and orientation in space was shown [*Sarkisian V., 2000*]. In respect to the afferent control of LVN neurons activity it is of interest to study the mechanisms of vestibular-autonomic reflexes and particularly interrelations of LVN with hypothalamic neuroendocrine centers such as paraventricular (PVN) and supraoptic (SON) nuclei of hypothalamus [*Hermes M. et al., 1996; Cui L.-N. et al., 1997*]. Neurons of PVN receiving bilateral vestibular afferents gain the vestibular stimuli to participate in the integration of vestibular-autonomic reflexes [*Liu F. et al., 1997*]. Moreover, the study on differences in participation of four vestibular nuclei in vestibular-autonomic reflex in case of their stimulation effects on the neurons of posterior hypothalamic field allowed to draw a conclusion on vestibular information transfers to them after being mainly processed in the superior (SVN) and lateral (LVN) vestibular nuclei [*Inokuchi A. et al., 1986*]. The discovered direct connections of LVN with PVN and SON indicate that LVN acts not only as an integrative strucrure participating in coordination and control of various motor actions related to the regulation of posture and spatial orientation [*Sarkisian V., 2000*], but is also involved in the processes of central regulation of autonomic functions. The effects of LVN stimulation towards the neuronal activity of the lateral hypothalamic field (LHF) was studied in rats by means of *in vivo* extra- and intracellular registration technique. As far as LHF is in close connection with regulation of autonomic nerve activity, demonsration of the polysynaptic pathways in the given projection testifies to functional involvment of LHF in the vestibulo-autonomic responses [*Katafuchi et al., 1994*].

The availability of biochemical heterogenic projections to the PVN and SON is of interest. In rats distribution and source-cells (about 3 in the midbrain) of serotoninergic inputs to PVN and SON are described [*Sawchenko P., Swanson L.,1983*]. Organization of a number of central noradrenergic pathways with specific subdivisions of PVN and SON through interconnection with the nucleus of solitary tract (accepting primary visceral sensor information), ventral lateral medulla, and *locus caeruleus* was also shown. This loop may play an important role in the integration of hypothalamic responses to visceral stimuli, thus participating in autonomic and neuroendocrine modes of haemostatic control [*Sawchenko P., Swanson L., 1981*]. Noradrenergic projection to the hypothalamus, partially mediated by internuclear glutamatergic excitatory interneurons, has a critical role in centripetal control of vasopressin and oxitocin production [*Daftary S. et al., 1998*]. The phasic burst discharging of single PVN neurons responding to intero- and exteroceptive stressors in freely moving awake rats presumably are vasopressin-secreting neurons [*Watanabe S. et al., 2004*].

Finally, one should mention the complex intrahypothalamic connections of PVN [*Hermes M. et al., 1996*] and SON [*Cui L.-N. et al., 1997*] reflecting numerous physiological factors, which participate in generation of "daylight" and "night" rhythms and are recognized as hypothalamic neuroendocrine centers. Particularly, mentioned rhythms are accompanied by changes in physiological manifestations such as hormone releasing,

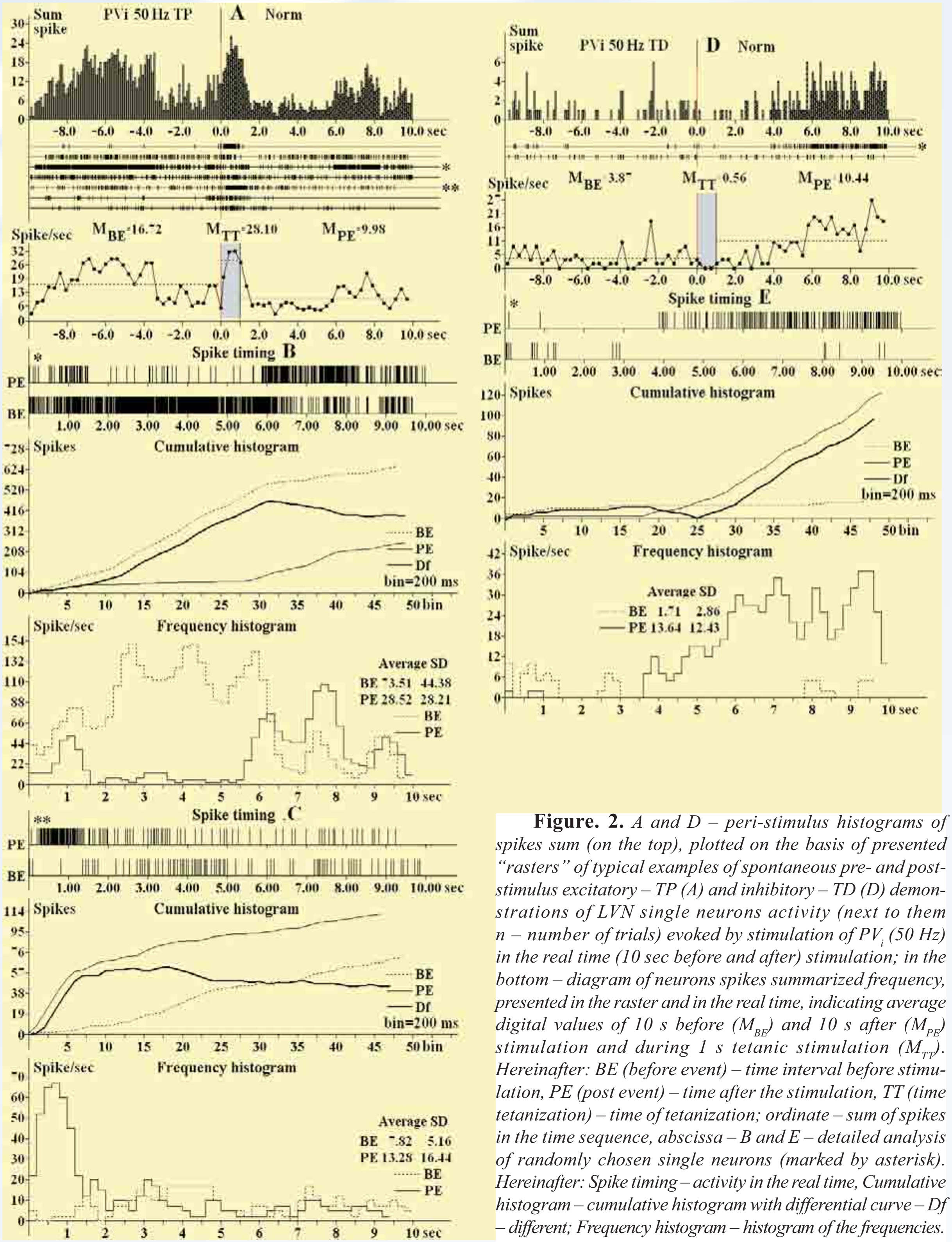

Figure. 2. *A and D – peri-stimulus histograms of spikes sum (on the top), plotted on the basis of presented "rasters" of typical examples of spontaneous pre- and post-stimulus excitatory – TP (A) and inhibitory – TD (D) demonstrations of LVN single neurons activity (next to them n – number of trials) evoked by stimulation of PV_i (50 Hz) in the real time (10 sec before and after) stimulation; in the bottom – diagram of neurons spikes summarized frequency, presented in the raster and in the real time, indicating average digital values of 10 s before (M_{BE}) and 10 s after (M_{PE}) stimulation and during 1 s tetanic stimulation (M_{TT}). Hereinafter: BE (before event) – time interval before stimulation, PE (post event) – time after the stimulation, TT (time tetanization) – time of tetanization; ordinate – sum of spikes in the time sequence, abscissa – B and E – detailed analysis of randomly chosen single neurons (marked by asterisk). Hereinafter: Spike timing – activity in the real time, Cumulative histogram – cumulative histogram with differential curve – Df – different; Frequency histogram – histogram of the frequencies.*

rhythms of metabolic processes, body temperature, etc. [*Saeb-Parsy K. et al., 2000*]. Connections of magnocellulr SON [*Cui L.-N. et al., 1997*] and PVN [*Hermes M. et al., 1996*] neurons with superior chiasm nucleus (SCN) that generates the majority of biological rhythms in mammals were shown electrophysiologically to be underlying these rhythms. The reciprocal connections of SON with PVN [*Zanchetti A., Zaccolini A., 1954; Swanson L. et al., 1981; Moore R., 1995*] and SON [*Saeb-Parsy K. et al., 2000*] were also shown. The projections of arcuate nucleus to SON [*Leng G. et al., 1988*], and connections of PVN and SON [*Saphier D., Feldman S., 1985*] were demonstrated as well. Alongside with the best studied intrahypothalamic connections of SON and PVN, data concerning their biochemical heterogenic [*Sawchenko P., Swanson L., 1982*] descending projections to the spinal cord (SC) neuronal elements are quite scarce [*Hosoya Y., 1980*; *Swanson L., Kuypers H., 1980*]. The predominant representation of PVN in SC should be mentioned. The magnocellular SON neurons project to SC in a lesser degree, although they have similar physiological functions and afferent connections with PVN [*Sawchenko P., Swanson L., 1983*].

In this study besides the further investigation on peculiarities of vestibular-hypothalamic projections for elaboration of Deiters' neurons nuclei model meant for morphological-functional study under conditions of unilateral labyrinthectomy (UL), an intensive analysis of LVN single neurons pulse of flow frequency activity evoked by bilateral high frequency stimulation of hypothalamic PVN and SON nuclei in intact animals was carried out.

Materials and Methods

Experiments were carried out in 7 intact adult male Albino rats (230±30 *g*). During acute experiments animals were immobilized by 1% dithylinum (25 *mg/kg,* i/p) and under artificial ventilation the section of SC at T_1-T_3 level (with ultrasound scalpel) was done to achieve *encephale isole* preparation*, i.e.* awake brain. In stereotaxic apparatus the trepanation of the skull was done from *bregma* till *lambda* and *dura mater* was removed. Stereotaxic orientated glass electrodes of 1-2 µ tip diameter were filled with 2 M NaCl and inserted into LVN for bilateral recording of single neurons spikes flow activity evoked by bilateral multiple stimulation of *ipsi-* (i) and contralateral (c) $PVN_{i,c}$ and $SON_{i,c}$ (rectangle current pulses - 0.05 *ms*, 0.12-0.18 *mV*, 0.32 *mA* and frequency of 50 and 100 *Hz* during 1 *s*). Stimulating electrodes were inserted according to stereotaxic coordinates of the rat atlas [*Paxinos G., Watson C., 2005*]: SON (AP – 1.3, L ±1.8, DV+ 9.4 *mm*); PVN (AP – 1.8, L±0.6, DV+7.8 *mm*). The recording electrodes were inserted by coordinates: AP -11.5, L±2.5, DV+7.0 *mm*. Post stimulus activity was revealed as tetanic potentiation (TP) and depression (TD) following with posttetanic potentiation (PTP) and depression (PTD) of different latency, intensity, and duration. After special selection, the pulse flow was analyzed by means of special mathematical program before and after stimulation for getting "rasters" of single neurons pre- and post stimulus spike flows in real time and on their basis a number of histograms was arranged: summary, peri-event time histograms (PETH), cumulative histograms and frequency histograms. By means of selected comparable groups of neuronal spiking the similar complex averaged peri-stimulus (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 computer program (developer: V.S. Kamenetski) allows to separate stimuli, superposed on action potential (AP) during their close succession in the process of TP and TD and avoid traditional complex intracellular recording approach of long-term tetanic potentiation and depression. The requirement of mentioned approach becomes more significant due to the relevance of TP and TD inventory as a constant revealing of post stimulus activity in comparison with less stable post tetanic potentiation (PTP) and depression (PTD). At the end of each experiment the sites of stimulation and registration were verified histologically.

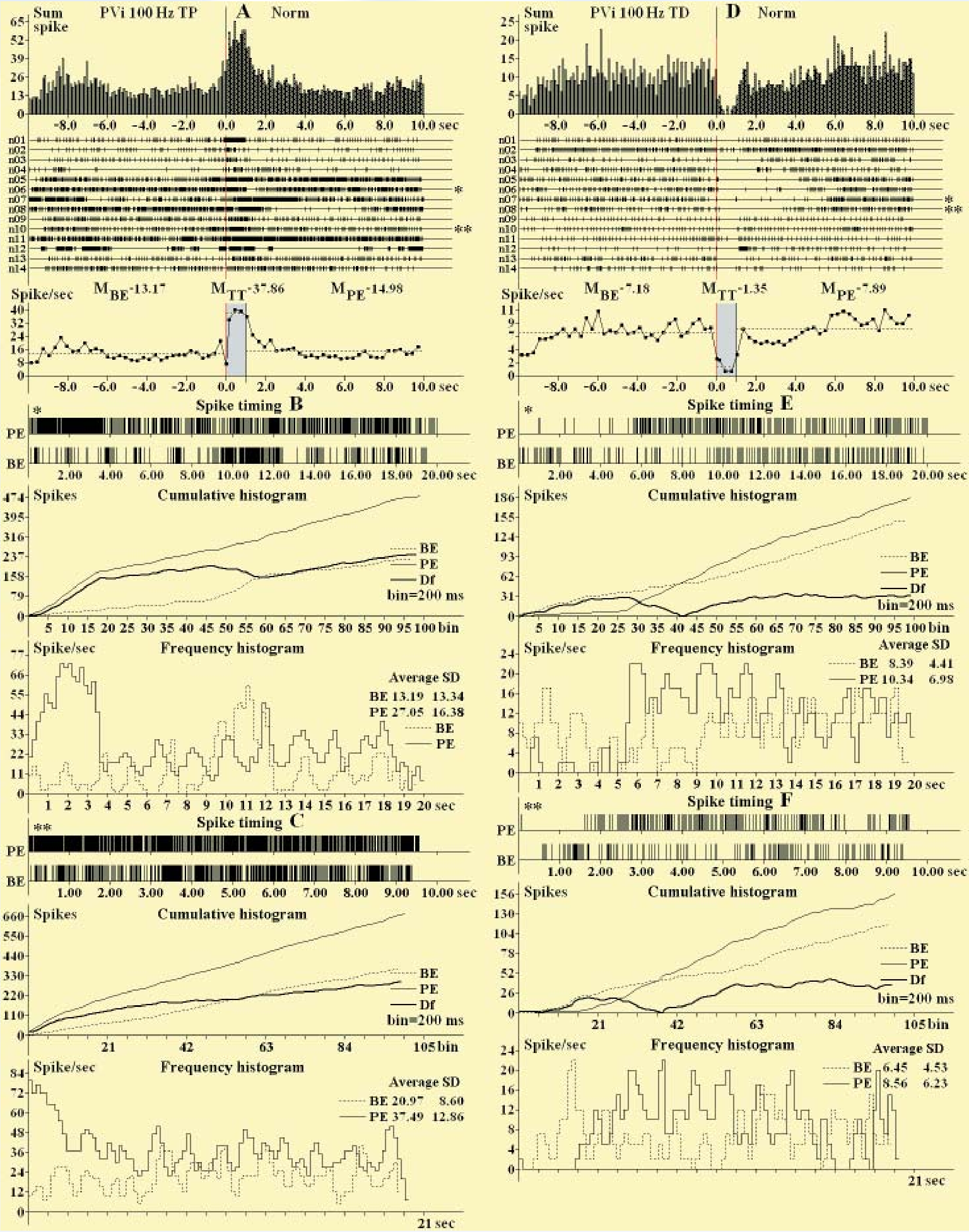

Figure 3. *A and D – peri-stimulus histograms of spikes sum (on the top), plotted on the basis of presented "rasters" of pre- and post-stimulus excitatory – TP (A) and inhibitory – TD (D) demonstrations of LVN single neurons spike activity (next to them n – number of trials) evoked by stimulation of* PV_i *(50 Hz) in the real time (10 s before and after stimulation); in the bottom – diagram of single neurons spikes summarized frequency, presented in the raster. B, C and E, F - detailed analysis of randomly chosen single neurons (marked by asterisk).*

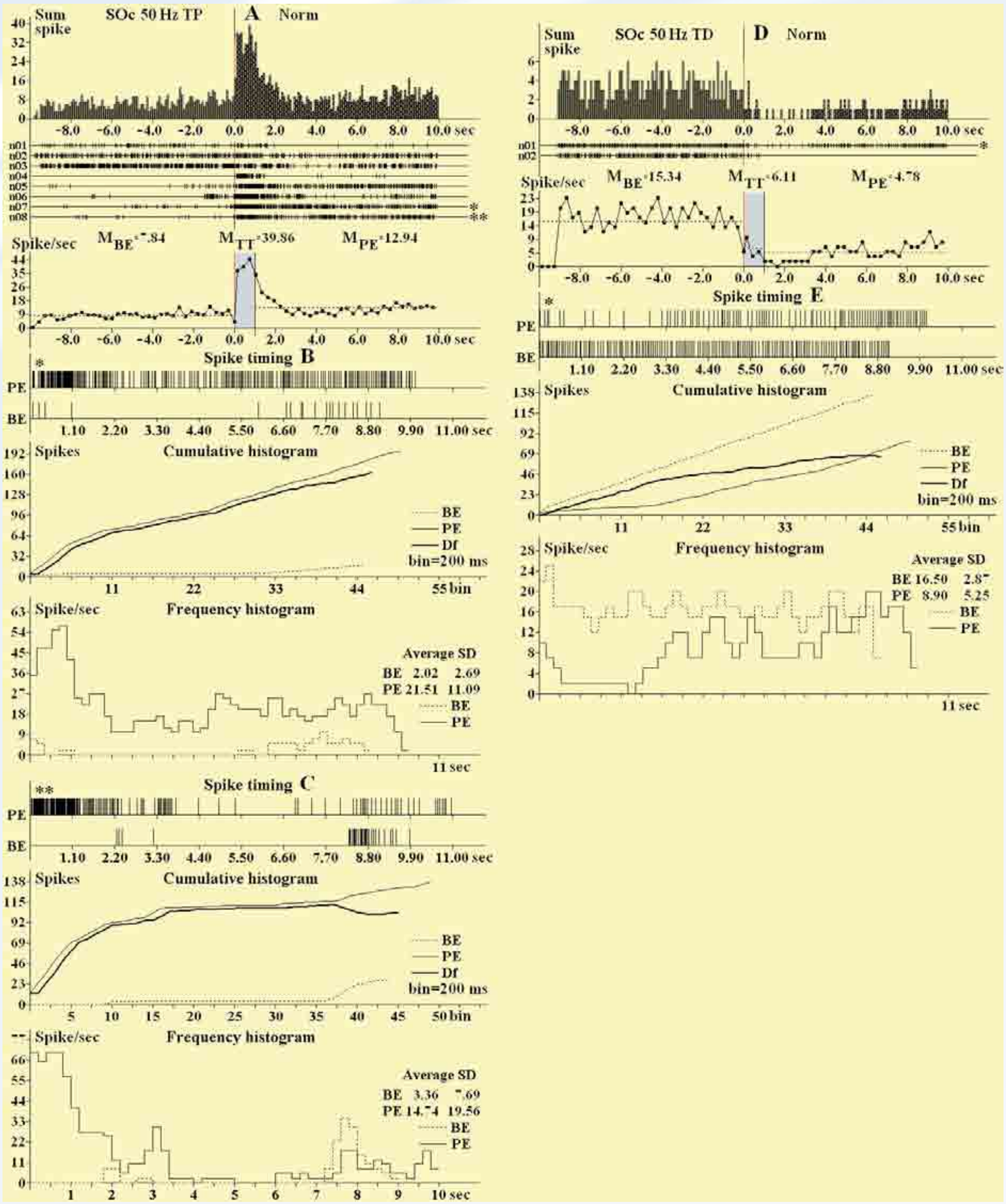

Figure 4. *A and D - peri-stimulus histograms of spikes sum (on the top), plotted on the basis of presented "rasters" of pre- and post-stimulus excitatory – TP (A) and inhibitory – TD (D) demonstrations of LVN single neurons spike activity (next to them n – number of trials) evoked by stimulation of SO_c (50 Hz) in the real time (10 sec before and after stimulation); in the bottom – diagram of single neurons spikes summarized frequency, presented in the raster. B, C and E - detailed analysis of randomly chosen single neurons (marked by asterisk).*

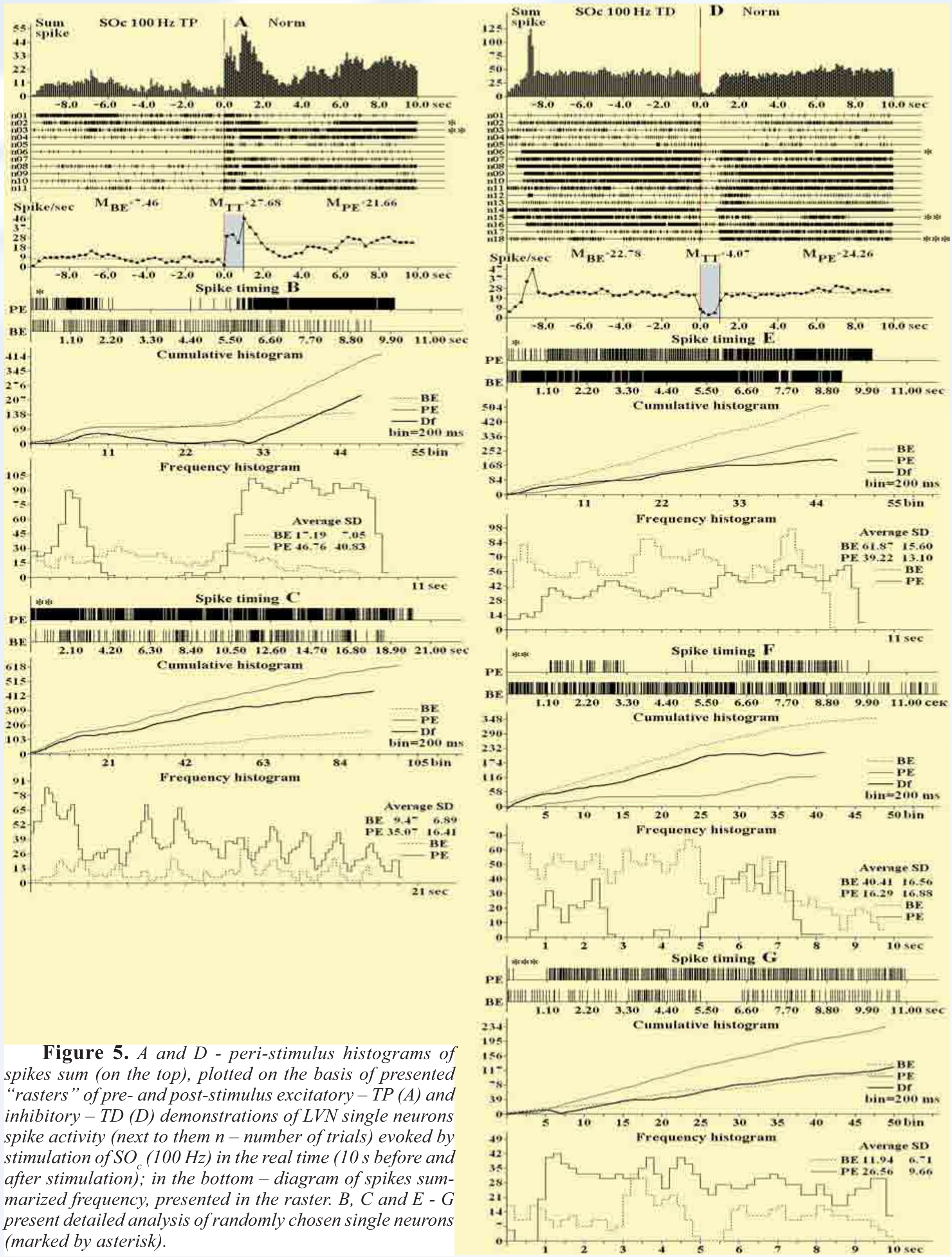

Figure 5. *A and D - peri-stimulus histograms of spikes sum (on the top), plotted on the basis of presented "rasters" of pre- and post-stimulus excitatory – TP (A) and inhibitory – TD (D) demonstrations of LVN single neurons spike activity (next to them n – number of trials) evoked by stimulation of SO_c (100 Hz) in the real time (10 s before and after stimulation); in the bottom – diagram of spikes summarized frequency, presented in the raster. B, C and E - G present detailed analysis of randomly chosen single neurons (marked by asterisk).*

For histochemical investigation parts of the brain stem were fixed for 2-3 days in 5% neutral formalin prepared on phosphate buffer. The frontal frozen sections (40-50 μM) were processed using the new approach of revealing the activity of Ca^{2+}-dependent acidic phosphate developed by I.B. Meliksetyan [*Meliksetyan I., 2007*].

After washing the sections were developed in 3% solution of Na_2S and covered with Canadian balsam. The connections of PVN and SON with LVN were studied in a separate experiment using HRP method of retrograde transport.

Results

The study on impulse activity flow of single LVN neurons evoked by bilateral stimulation of PVN and SON was carried out in spinal rats in norm. There were recorded 128 neurons.

Electrophysiological study.

The following 6 figures present histograms reflecting results of averaged electric activity of LVN neurons evoked by stimulation of PVN and SON (Figure 1), rasters of activity of voluntary chosen neurons, as well as detailed analysis of neurons activity (Figures 2-5). As a whole, both excitatory and inhibitory effects were revealed in response to bilateral stimulation of PVN and SON

Stimulation of the PVN_c (PV_c) at frequency of 50 *Hz* evoked post stimulus effects on PETH in the shape of tetanic potentiation (TP – Group A) and depression (TD – Group B), which almost two times exceeded the level of background activity in case of TP and was two times lower that of TD (up to 0) with subsequent stabilizing the activity up to pre-stimulus level (Figure 1A). The same can be seen on the next cumulative (Figure 1B) and frequency histograms (Figure 1C). The stimulation of PV_c at frequency of 100 *Hz* led to generation of TP (Group B) and TD (Group D), which differ from pre-stimulus level in the range of 2.6 and 6.5 times, respectively (Figure 1A). As to the effects of PVN_i (PV_i) stimulation at frequency of 50 *Hz*, in PETH there was TP (Group A) and TD (Group B) with exceeding and dropping of activity in comparison with the initial level in the range of 3 and 1.6 times, respectively, but reaching only the pre-stimulus level after TD with the subsequent late PTP (Figure 1D). PV_i stimulation at frequency of 100 *Hz* evoked TP (Group B) and TD (Group D) respectively higher and lower than pre-stimulus level of activity for 2.8 and 3 times, followed by stabilization of activity (Figure 1D). The same can be seen on the cumulative and frequency histograms (Figures 1E and 1F). The stimulation of SON_c (SO_c) at frequency of 50 *Hz* evoked TP and TD on PETH in the following limits of exceeding and decreasing from the pre-stimulus level for 2.8 and 3 times, respectively, while in case of 100 *Hz* the range was about 2.4 and 7 times for TP and TD, respectively. Moreover, depression achieved 0 and post stimulus activity stabilized up to the end of trial except the late PTP after stimulation at 100 *Hz* with the following stabilization of post stimulus activity displays in all trials. The stimulation of SO_i at frequency of 50 *Hz* leads to producing TP and TD in the range of 8 and 1 time, respectively. The stimulation at 100 *Hz* initiates TP and TD up to 2.3 and 7 times, respectively. In this case, stimulation at frequency of 100 *Hz* evoked late PTP with the following stabilization of activity. In both described cases post stimulus activity from $SO_{c,I}$ nucleus i.e. from both sides underwent similar shifts. As a whole, no significant changes were registered in relation to the side of stimulation. Therefore, only data on unilateral stimulation are presented in the rest of figures .

Figures 2-5 reflect the above mentioned effects by the example of summarized raster frequency of spiking and detailed analysis of distinctive examples of studied neurons under stimulation at frequency of 50 *Hz* (Figures 2 and 4) and 100 *Hz* (Figures 3 and 5), as well as the genesis of excitatory (A-C) and inhibitory (D-G) reactions from PVi (Figures 2 and 4) and SOc (Figures 3 and 4).

Figures 2 and 3 show detailed analysis of above mentioned effects of PVi stimulation of randomly chosen neurons excitatory (Figure 2A-C) and inhibitory (Figure 2 D;E) effects at frequencies of 50 *Hz*, as well as of those at stimulation frequencies 100 *Hz* (Figures 3A-F), respectively.

Figures 4 and 5 demonstrate corresponding

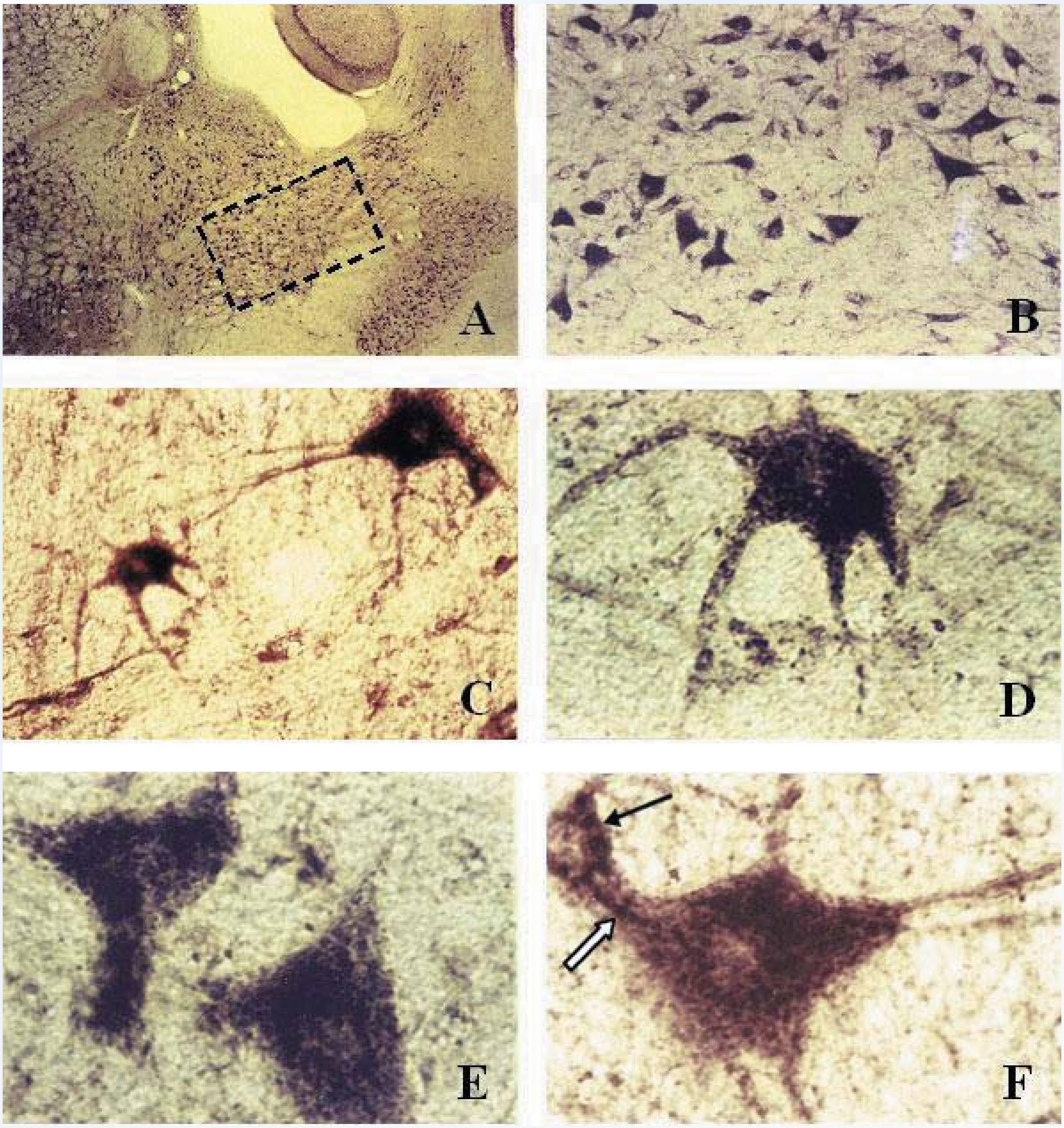

Figure 6. A – *LVN of an intact rat (rectangle). B – Fragment of A at high magnification: gross granule suspend of plumbum phosphate is uniformly distributed in the soma and dendrites. The zone of cytoplasm surrounding the nucleus (E, F) stains most darkly. By moving away from the cell body suspend in processes is located less densely (D). In most of neurons the processes can be traced far from the cell body with a few branches in the given plane of the section (C); F – small cell (black arrow), in close vicinity with process of the large cell (white arrow). Magnification: 25 (A); 160 (B); 400 (C); 1000 (D-F)*

effects of SOc stimulation: the excitatory (Figure 4A-C; Figure 5A-C, respectively) and inhibitory (Figure 4D;E; Figures 5D-F, respectively) at stimulation of 50 and 100 *Hz*.

Morphological study.

Among bundles of internal part of cerebellar peduncles the large polygonal cells sometimes of extended form compose LVN (Figure 6A). Neurons of LVN have high activity towards acidic phosphate. The large polygonal nerve cells (Figure 6B) revealed by Nissl method contain intensively labeled gross granules of plumbum phosphate suspends similar to tigroid.

In cytoplasm the zone surrounding nucleus stains most darkly (Figures 6E;F), whereas in processes the suspend is localized less densely (Figure 6D). The large cell bodies smoothly turn to thickened dendrites, which without branching can be traced in plain of the given section at some distance from the body (Figure 6C).

The existence of direct projections of SON and PVN to LVN was demonstrated by means of HRP method of axonal retrograde transport (Figure 7). According to their topographic distribution labeled SON cells were observed in the medial and ventral parts of the nucleus. The population of labeled source-cell projections to LVN significantly differs from the large neurosecretory SON cells in their small sizes. On the contrary, labeled PVN cells were large in size and distributed in the dorsal and medial divisions of a nucleus. In mentioned nuclei the passing fibers, apparently as an anterograde labeled pre-terminals, were also observed.

Discussion

Results of the present study indicate to the presence of excitatory and inhibitory post stimulus development of LVN neurons activity to stimulation of PVN and SON with different sequence, intensity, duration and latency of onset. The fact of permanent presence of post stimulus activity of LVN neurons depressive effects or TD, as well as early and late PTP is of interest. Moreover, depressive effects and particularly tetanic ones can be of very different origin: real inhibition or even disfacilitation. The purpose of this study was not only the analysis of depression mechanisms but the fact of LVN neurons inhibition from structures related to the regulation of autonomic functions. The importance of providing the mentioned depression by higher brain endocrine centers, such as PVN is expected by permanent necessity not only to control LVN activity realized through brain motor centers when their activity predominance may accrue upset of motor flexor-extensor balance, but also the autonomic displacements following the possible intensification of vestibular tonus. Moreover, the existence of excitatory reaction indicates to delicate regulatory influence of PVN and SON on the vestibular complex. Earlier in a series of intracellular experiments it was shown that stimulation of numerous brain structures (cerebellum, spinal trigeminal nucleus, lateral reticular nucleus, inferior olive, posterior hypothalamus, etc.) evoked inhibitory postsynaptic potentials (IPSP) in Deiters' neurons [*Sarkisian V., 2000*]. Moreover, LVN being permanently under the inhibitory action of different brain structures preventing predominance of the extensor tonus is in permanent default of excitatory input. Hence, depression of LVN neurons cannot be the result of disfacilitation and/or pseudo-hyperpolarization origin (in the basis of which underlies a high level activity initiated by powerful excitatory input that prevents membrane potential return to its initial level) and is typical for cerebello-spinal [*Llinas R., 1964*] and iterpositar-rubral projections [*Toyama K. et al., 1968*], on the level of which this phenomenon was described. However the possible mechanism of disfacilitation during registration of pseudo hyperpolarization can not be completely excluded. Earlier we have shown that besides IPSP stimulation of spinal trigeminal nucleus also evoke in Deiters' neurons strong disfacilitatory responses (with latency of 2.5±1.1 *ms* and amplitude 10.7±4.9 *mV*) [*Fanardjian V., Sarkisian V., 1988*]. By their characteristics these hyperpolarizing potentials are similar to those of above mentioned first described when studying the influence of cerebellum on spinal extensor motor neurons and red nucleus neurons [*Terzuolo C., 1959; Llinas R., 1964;*

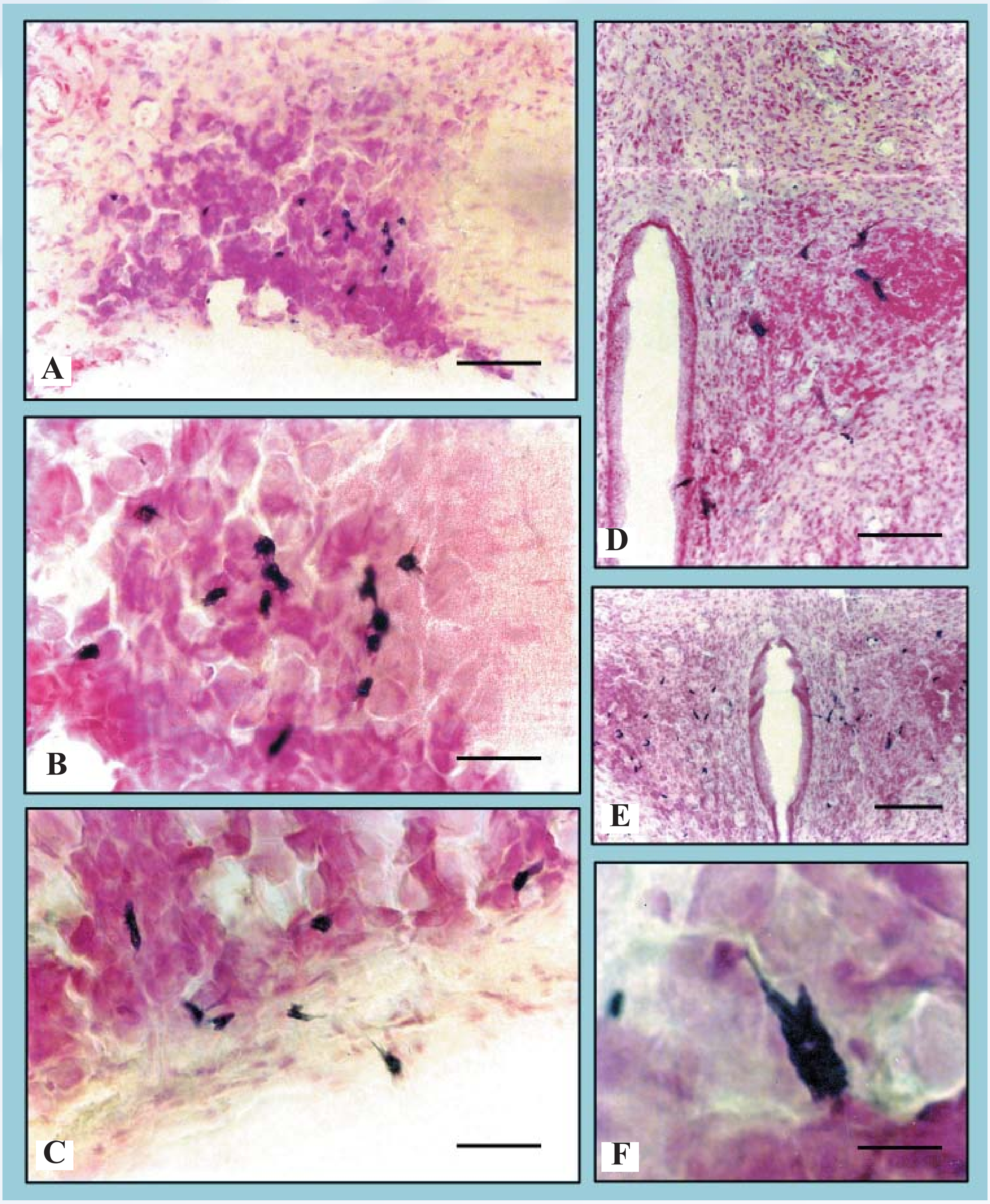

Figure 7. *Photomicrography of cells retrograde marked by HRP in SON (A, B, C, F) and PVN (D, E) of the hypothalamus following injection of marker in the lateral vestibular nucleus of Deiters'. In E – marked cells on the right of the third ventricle, on the left – marked fibers (possibly pre-terminals). Scale: A, E - 200 µ; B, C – 50 µ; D – 120 µ; F – 20 µ. Method of Mesulam.*

Toyama K. et al., 1968]. In earlier studies there are data on involvement of cerebellum in regulation of some non-somatic activities through cerebellar-hypothalamic projections. The electrophysiological study also elucidated predominantly inhibitory mono- and polysynaptic excitatory inputs from cerebellar fastigial nucleus to PVN neurosecretory cells, the repetitive stimulation of which led to decrease of activity that sometimes resulted in rebound activity [*Katafuchi T., Koizumi K., 1990*]. As to the interrelations of LVN and fastigial nucleus it was shown that neurons of this latter receive excitatory input from ipsilateral VIII nerve and bilateral secondary excitatory projections from LVN [*Sarkisyan V., Simon L., 1982; Fanardjian V., Sarkisian V., 1988a*]. On the other hand, the existence of polysynaptic excitatory and inhibitory connections of VIII nerve with PVN and SON is documented [*Azzena G. et al., 1993*]. The mentioned cerebellar-hypothalamic loop is involved in regulation of neuroendocrine system, particularly in osmostatic reflexes and defense reactions [*Zanchetti A., Zaccolini A., 1954*]. Finally, it was shown that afferents from interpose nucleus of cerebellum to PVN neurons include those of baro- and osmo-reflex sensitive ones, indicating an active role of the cerebellum in cardiovascular regulation through the mentioned projections [Wen Y. et al., *1998*]. Ultimate discovery of TD mechanism is the subject of our subsequent intracellular investigations. Nevertheless, the existence of excitatory besides depressor tetanic and post tetanic post stimulus changes of pulse activity flow frequency in LVN neurons in response to PVN and SON stimulation requires evaluation of their mechanisms of origin. According to recent data, it is assumed that GABA and glycine may play a significant and/or perhaps varying role in developing and mature central vestibular system [*Tighilet B. and Lacour M., 2001* and others]. Recently there was presented a new regulatory mechanism in fast CNS synapses involving L-type potential-depended Ca^{2+} channels, which do not participate in low frequency release of transmitter but have contribution to accumulation of presynaptic Ca^{2+} during high frequency activity. This promotes the release of vesicles during tetanic stimulation, as well as intensifies the probability of transmitter releasing in post-tetanic period being completed by PTP manifestation. The results were obtained during registration of GABA-ergic IPSP from hippocampus cell culture in conditions of applying baclofen as the inhibitor of N and P/Q type potential-depended Ca^{2+} channels leading to thrice amplification of PTP. Moreover, in the basis of PTP there is accumulation of Ca^{2+} in presynaptic terminal in the period of GABA-ergic neuron tetanic stimulation, which leads to intensification of vesicles release up to 1 *min* [*Jensen K. et al., 1999*]. Of interest is the fact that in some systems during development of nervous system GABA acts as trophic factor influencing various events including proliferation, migration, differentiation, maturing of the synapse, cellular death and expression of $GABA_A$ receptor [*Owens D., Kriegstein A., 2002*]. Finally, there was demonstrated the modulatory action of histaminergic system on neurotransmission in vestibular nuclei and changes in its plasticity course, particularly through inhibition of GABA releasing both by means of direct influence on presynaptic H(3) receptors (probably localized on GABA-ergic terminals) and through indirect path, involving increased releasing of glycine by activation of post-synaptic H(1 and 2) receptors (probably on glycine-ergic neurons) [*Bergquist F. et al., 2006*].

In other words, the involvement of real GABA-ergic inhibition during TD may not be excluded. The observed direct connections of LVN with PVN and SON indicate that LVN acts not only as an integrative structure participating in coordination and control of different motor actions, which provide regulation of posture and orientation in space [*Sarkisian V., 2000*]; LVN is involved in the central regulation of autonomic functions as well.

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