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Synaptic Processes in Raphe Magnus Nucleus under Activation Periaqueductal Gray Matter on the Model of Parkinson's Disease

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ABSTRACT

The electrophysiological studies on 4 Albino rats (230 ± 30г.) on the rotenone model of Parkinson's disease (PD), induced by unilateral injection of rotenone and kept 4 weeks has been conducted. The extracellular on-line recording of spike activity of 149 single neurons of the Raphe Magnus (RMG) at high frequency stimulation (HFS) of Periaqueductal gray (PAG) had produced. The programmed mathematical analysis of spikes averaged frequency, with recalculation in interpulse intervals and frequencies to assess of degree of manifestation depressor and excitatory effects as well as the frequency of pre- and post-stimulus activation degree of manifestation in terms of diagrams of averaged frequency spikes are used. On the model of PD a significant reduction in quantity of RMG neurons, evoked at HFS PAG by depressor and depressor–excitatory manifestations of activity had been revealed. On the model of PD, the significant reduction in the number of neurons RMG, responding at PAG HFS by depressor and depressor-excitatory manifestations of activity has been revealed. Analysis of relative degree of intensity of depressor and excitatory effects, by way of example diagrams average frequency of spikes, led to the conclusion. It has been discovered the prevalence of excitatory post stimulus manifestations of activity over depressive (on the order of 1.63- and 2.0-multiple). The pre stimulus frequency of activity substantially prevailed in neurons, responding by excitatory effects (on the order of 2.46- and 17.0-multiple in uni- and multidirectional successions, respectively). As regards to post stimulus frequency, the difference is even higher proved– on the order of 14.6 and even 56.5-multiple for uni- and multidirectional sequences, respectively. Besides, especially larger for multidirectional successions. In other words, under PD excitotoxicity revealed, promoting the powerful frequency growth of pre- and post-stimulus activity in both excitatory sequences, testifying about deep neurodegenerative defeat of important ant nociceptive structure – RMG and promotes the emergence of resistant chronic pain.

Keywords

Rotenone model of Parkinson's disease, Unilateral damage of substantia nigra compacta, Single neuronal activity of Raphe Magnus, High frequency stimulation of Periaqueductal gray.

Introduction

Neurodegenerative disease (ND) is social, medical and economic problem and constitute the main areas of interest to neurologists. In addition, life expectancy is inevitably accompanied by an increase in ND. The most common ones are prevalent with age, accompanied by progressive motor and cognitive impairment [1]. Among them, we should mention Alzheimer's disease (AD) and other dementias, Parkinson's disease (PD), moto neuronal disease, Huntington's disease, spinocerebellar ataxia and spinal muscular atrophy. In this case, the pain that accompanies most ND has become an important element of consideration in clinical practice and, despite intensive research, still remains unexplored [1]. Pain at ND largely presented in PD, amyotrophic lateral sclerosis and chronic hereditary neuropathy [1]. Motor and sensory deficit may directly cause pain when amyotrophic lateral sclerosis, PD, cerebral spinal ataxia and hereditary neuropathy, where subjective expression can be restricted motor deterioration. Even when AD, pain is

not a secondary issue and worthy of serious consideration. Less frequently, such as when the Huntington's disease, an expression of pain may be restricted. In addition, pain is one of the non-motor symptoms of PD, most often faced by patients, often unrecognized and inadequately treated, in contrast to motor symptoms. However, the pathophysiology of abnormal is not installed when PD nociceptive mechanisms, predisposing to the development of spontaneous pain. This is confirmed by the psychophysical and neurophysiological studies of PD patients without pain [2], with the reduction of the thresholds of different pain modalities [3], even in the early stages [4]. When PD provided motor and non-motor symptoms, pain experienced by approximately 30-50% of patients. There is no consensus regarding the pathophysiological mechanisms, classification and potential risk factors of pain when PD [5]. The complex mechanism of pain in PD is associated with pathological changes in brain structures involved in nociceptive mechanism. Potential risk factors of pain with PD include age, sex, and duration of illness [5]. Further study of the mechanisms of formation to improve pain management in patients with PD [5].

Finally, when PD shows the reduction of thin no myelinated fibres [6,7]. In other words, there is no available systematic study on treatment of pain of PD, strictly dependent from the type of pain, and it is limited to non-opioid analgesics, opioids, antidepressants and/or anticonvulsant means [8]. It should also be noted the analgesic effect of deep brain stimulation, which is shown to improve motor symptoms [7], including positron emission tomography, uncovered the reduced brain activity associated with pain [1]. As a result, generally, insufficient attention has been given to pain, and therapeutic strategy is based primarily on symptomatic approaches (analgesics, anti-inflammatory), without systematic consideration of causal mechanisms. The latter will provide the prospect of participation neurologists in pain management, taking into account its causes and mechanisms, focusing on predisposing factors, promoting successful pharmacological and non-pharmacological tests.

The pain to neurons of the brain higher centers transmits two pathogenically certain systems, medial and lateral. Medial system involved in affective and cognitive assessment measuring pain, pain memory and autonomic responses. Lateral system important for sensory-discriminative component of pain, provides information about the localization and duration of pain [9-12]. Descending pathways that occur in the brain stem and cerebral structures play an important role in integrating and modulation nociceptive information in the dorsal horn. The main components are serotonergic, noradrenergic and dopaminergic (DAergic) network. These paths can be enhanced or reduced sensitivity of neurons in the dorsal horns [10]. PD as multifocal and progressive degenerative disease may strike a painful process at multiple levels, from the transfer of pain from peripheral structures to higher centers to their perception and interpretation, as well as interference with various anatomical structures to be manipulated in the mechanism of pain [5]. Braak et al. [13,14] to understand the changes occurring in the anatomical structures of pain associated with higher centers, during the flow of PD, subdivided in 6 periods of its development. The changes typical of the pre-motor period start in the olfactory bulb and progress toward the inferior brain stem area (including the medulla oblongata and pontine tegmentum) of Lewy neurites and Lewy bodies (period 1–2). In the following symptomatic periods, pathologic changes take place in the mid brain including the substantia nigra (SN) (period 3), the meso-cortex (period 4), and finally the neo-cortex (periods 5–6) [13,14]. Nociceptive information cannot be transmitted directly from the spinal cord to higher centers[14,15], since the descending pathways involving various brain stem nuclei modulate it. Some of these nuclei are affected early in PD [10]. When examining the brain stem in PD, it is observed that rostro medial medulla, comprising the nucleus raphe Magnus (MRG) and gigantocellular reticular nucleus, starts to be affected in period 2 of PD. This area is important for its role in the descending regulation of pain since it is the last station of the descending anti-nociceptive pathways [16,17].

The locus cerulean plays a role in the nociceptive modulation within the thalamus [18]. Consequently, the presence of Lewy bodies in the cerulean/sub-cerulean area, which also plays a role in the noradrenergic modulation of pain, as well as in intra-laminar and medial thalamic nuclei, could have an effect on autonomous, motivational-emotional and cognitive-evaluative responses [3,6,11-21]. Serotonergic input to the spinal dorsal horn from the caudal MRG affects the mechanisms of pain by facilitating the nociceptive transmission of the mechanical stimuli, and through such facilitation repressing the first reaction to neurologic inflammation and to the chemical activation of primary afferents [22]. The caudal raphe nuclei and the MRG, which are reciprocally linked [23], together with the cerulean/sub-coeruleus area, make up the functional gain-setting system. This system transforms important inputs from the higher-level components of the limbic lobe into descending projections by controlling the excitability of the spinal and medullary pre-motor and motor neurons of the somatic-motor system [24,25]. Together with the LC, the gigantocellular nucleus and the nuclei of the bulbar raphe, the Periaqueductal gray matter (PAG) and the parabrachial nuclei play an important role in the modulation of spinal nociceptive transmission, e.g., on inhibition of nociceptive stimuli coming from the dorsal horn neuron. A disturbance in this pain-inhibiting region could cause an increase in the sensation of pain [11].

The lateral thalamus, one of the higher centers important for pain mechanisms, also plays a major role in central pain. Denervation of the nigrostriatal system increases neuronal activity in the sub thalamic nucleus, the internal Globus pallidus, and SN pars reticulate. Hyperactivity in these areas leads to a strong inhibition of the lateral thalamic region, which can affect pain mechanisms in two different ways: 1) Disinhibition of medial spinothalamic-cortical pathways to the anterior cingulate cortex due to the disruption of the lateral spinothalamic-cortical pathway to the parietoinsular system [26]; 2) Inhibition of the lateral thalamus reducing localization, one of the sensory discrimination elements of pain.

The difficulty that patients have in localizing their pain symptoms supports this hypothesis. On the other hand, other properties of sensory discrimination become more sensitive to sensory stimuli [11]. This may explain the changes in pressure and thermal pain thresholds observed in PD. Animal studies analyzing the effects of basal ganglia and DA on sensory pathways and their contribution to sensory perception reflect the importance of this region for pain [15].

Nociceptive neurons within the SN may respond with suppression or enhancement of discharge frequency following noxious stimulation and have large receptive fields that often include the whole body. The large receptive fields of nociceptive nigral neurons have no major effect on the spatial localization of painful stimuli [15]. Some studies, however, have reported the importance of these neurons on the codification of noxious stimuli [27], indicating that certain nociceptive nigral neurons may play a relevant role in sensory discrimination [15]. Animal experiments have shown that stimulating the SN leads to nociceptive inhibition by activating the spinal cord neurons through DAergic pathways [28-31]. Based on the results of these studies, it could be postulated that involvement of the SN in patients with PD affects the discriminatory aspect of pain and behavioral pain responses. In addition, striatal neurons that respond to low-threshold somatosensory stimulation also have large cutaneous receptive fields [32] and can play a role in the localization of and the response to stimuli from circumscribed regions [33-35].

Multi-sensory inputs within the striatum lead to the view that this area plays a role in the coordination of behavioral responses by integrating sensory information conveyed by different sensory methods. The wide dynamic range of neurons, which exhibit low mechanical thresholds, are sensitive to somatosensory stimuli across a broad range of stimulus intensities and are maximally responsive to noxious stimuli as well, some nociceptive neurons within the striatum could be coding for the intensity of noxious stimuli. The ability of striatal neurons to receive nociceptive stimuli from a large receptive area might indicate that these structures do not play a role in the spatial localization of painful stimuli; the striatum may, act in concert with somatotopically-organized areas that are co-activated and provide precise spatial information for the next level of integration [15]. DA secretion during painful stimuli has been identified within the dorso-lateral striatum. This type of response depends on the subjective perception of pain intensity. Additionally, the ventral striatum is clearly related to the emotional dimension of the human pain process and expectation [36]. In conclusion, striatum involvement in PD could affect the emotional dimension of pain and the subjective perception of pain intensity.

With regard to the role of DA in the development of the pain of PD [37], with the introduction of DA psychological and neurophysiological abnormalities are not restored [2]. DA may also modulate pain at different levels including the spinal cord, thalamus, PAG, the basal ganglia and the cingulate gyrus [38]. Axons coming from key dopaminergic areas, such as the SN pars compacta, the ventral tegmental area and the hypothalamus project to neocortical, mesolimbic, nigrostriatal and tuber infundibular pathways. These pathways mediate different non-motor symptoms, e.g., cognition, sleep and pain [38]. Mendlin et al. [39] observed that serotonin was not secreted after blocking postsynaptic D2 receptors in rats. Serotonin secretion in the forebrain is dependent on intact local DAergic neurotransmission has an important role in the sensory and emotional properties of pain. A lesion of the striatum DA terminals can also modify pain transmission [40]. A significant reduction of the nociceptive delay and an acceleration of the initial and final periods of nociceptive stimulation have been observed with lesions of this area. This condition effectively increases the nociceptive stimuli [41]. These results reveal the importance of DA in pain transmission.

In the present study undertaken study the correlation of excitatory and depressor responses of RMG single neurons under stimulation of PAG on the model of PD, induced by unilateral rotenone administration.

Materials and Methods

Electrophysiological experiments on 3 rats Albino lines (230 ± 30г.) on the model of PD, induced by unilateral administration of rotenone and 4 weeks kept were performed. The rotenone administration carried out in conditions of pentobarbital anesthesia (40 mg/kg, i/p) the rate of 12 μg in 0.5 μl Dim Exide (with speed 0.1 μl/min) in “medial forebrain bundle” by coordinates of stereotaxic atlas [42] (AP+0.2; L ± 1.8; DV+8 mm). All experiments were performed according to the "rules of laboratory animal care" (NIH publications for № 85-23, revised in 1985), as well as specific guidance provided for the care of animals and the Committee of the national health and medical service (NIH publication for № 80-23, revised in 1996). In stereotaxic apparatus, trepanation of skull from bregma to lambda and dissecting the brain dura mater produced. The glass microelectrodes with diameter of tip 1-2 μM, filled 2M NaCl, inserted in RMG according to stereotaxic coordinates (AP-11.6; L ± 2.0; DV+10.3 мм) for extracellular recording of spike activity of single neurons. Implement of PAG HFS (rectangular current shocks of duration – 0.05 ms, by amplitude of 0.12–0.18 mV, current strength 0.32 mA and frequency 100 Hz during 1 sec) according to stereotaxic coordinates (AP-4.92; L ± 2.0; DV+5.7 мм). After the sustained of expiry of the mentioned period in animals with PD the extracellular recording of background and evoked spike activity of single neurons of RMG are produced. Operation carried out on anesthetized animals (urethane 1,2 g/kg i/p) in the next regular behind the sequence: fixing the skull in stereotaxic apparatus, craniotomy with the removal of bones from bregma to lambda and separate of dura mater. Previously animals immobilized by 1% Diethylene *(Suxamethonium iodide)* (25 mg/kg i/p) and transferred to artificial respiration.

The activity manifested in the form of tetanic depression (TD) and potentiation (TP), accompanied by a post tetanic depression (PTD) and potentiation (PTP). The analysis of single spike activity of

149 neurons of RMG are conducted. Post stimulus manifestations of activity evaluated the on-line registration and programmed mathematical analysis, allowing selection spikes amplitude discrimination, withdrawal the «raster» of peristimular spiking of neurons, build sum histograms and diagrams of average frequency spikes. Produced further multi-level statistic processing for pre- and poststimulus pieces of time. For elected compared groups of spiking built summed and averaged peri even time histogram (PETH Average) and frequency histogram (Frequency Average). The analysis of obtained data on specially developed algorithm produced, providing reliability peristimulus changing of inter spike intervals. The homogeneity of two independent samples controlled by the t–criterion of Students. With a view to improving statistical validity peristimulus changes inter spike intervals also two-sample Wilcoxon-Mann-Whitney criterion (Wilcoxon-Mann-Whitney test) was used as nonparametric, assessing the homogeneity of two independent samples. Since the number of recorded spikes were quite large (up to several hundreds of spikes per 20 second interval after the stimulus), a modification of this test was used, taking into account its asymptotic normality - z-test. Accounting of critical values in comparison of those normal distribution at a significance level of 0.05, 0.01 и 0.001 shows, that in most samples of spiking when HFS there is a statistically significant alteration at least 0.05 level of significance.

Results and Discussion

Extracellular recording of spike activity of single RMG neurons on the model of PD are produced (149 нейронов, n=4). By means the analysis based on the average number of spikes (PETH), with conversion in pulse separation intervals and frequencies in Hz (Frequency Average), compared with the prestimulus level, in this condition, the following changes of depressor and excitatory tetanic reactions (TD and TP) in both post tetanic successions (PTD and PTP) were found. In RMG neurons at PAG HFS the tetanic depression on the model of PD within 1.8- and 2.0-multiplereduction of prestimulus activity in both sequences, respectively was determined (Figure. 1 A, Groups A, B), and tetanic potentiation order 2.76- and 2.54-multiple exceeding the prestimulus activity in both sequences has been calculated (Figure 1B, Groups A, B). As regards of depressor post stimulus manifestations of RMG neurons at PAG HFS, if you have almost identical values, the number of neurons decreased repeatedly. There is an obvious excitotoxicity, promoting higher frequency pre- and post-stimulus activity in both sequences. Thus, neurodegenerative defeat RMG has been revealed.

In assessing the relative severity of excitatory effects, for example of diagrams of average frequency of spikes, derived on the basis of raster pre- and post-stimulus excitatory and excitatory-depressor uni- and multidirectional manifestations of spike activity of neurons on the model of PD, indicating the average numerical values in real time 20 sec before and after stimulation, including the time of HFS, obtained values, presented in the form of disk diagram for a better presentation of the degree of severity in the frequency display (in %) experimental data in Figure 3 (on the bases of Figure 2), which led to the following conclusion. The values of the tetanic depression in depressor and depressor-excitatory sequences of RMG neurons at PAG HFS and values tetanic potentiation in excitatory and excitatory-depressor sequences in comparison with prestimulus level of activity differed enough (1.91- against 3.12- and 1.25 against 2.54-multiple, for uni- and multidirectional depressor and excitatory effects, respectively) (Figure 3), that testifies to the predominance of excitatory manifestations of activity over the depressant (order 1.63- and 2.0-multiple).

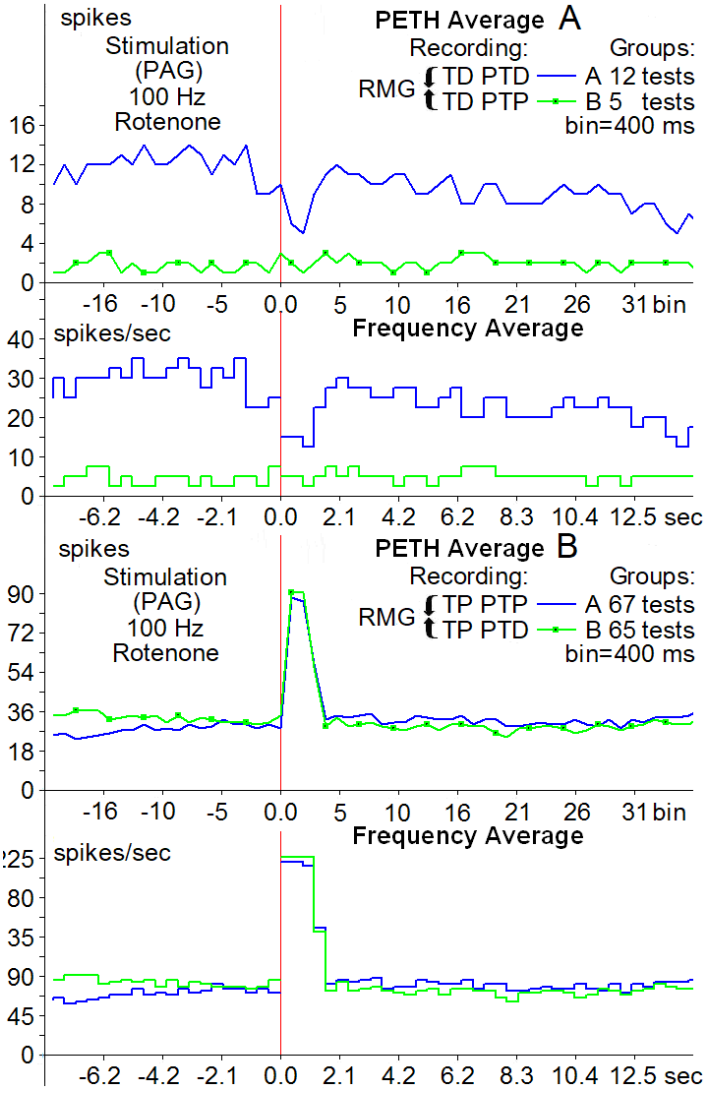


Figure 1: Average Peri-Event Time (PETH Average) histograms and histogram of frequency (Frequency Average) of depressor, depressor-excitatory (A, Groups A, B), excitatory and excitatory-depressor (B, Groups A, B) poststimulus manifestations activity of RMG neurons on the model of PD at PAG HFS (100 Hz, 1 sec) PAG. For groups the number of tests has been shown.

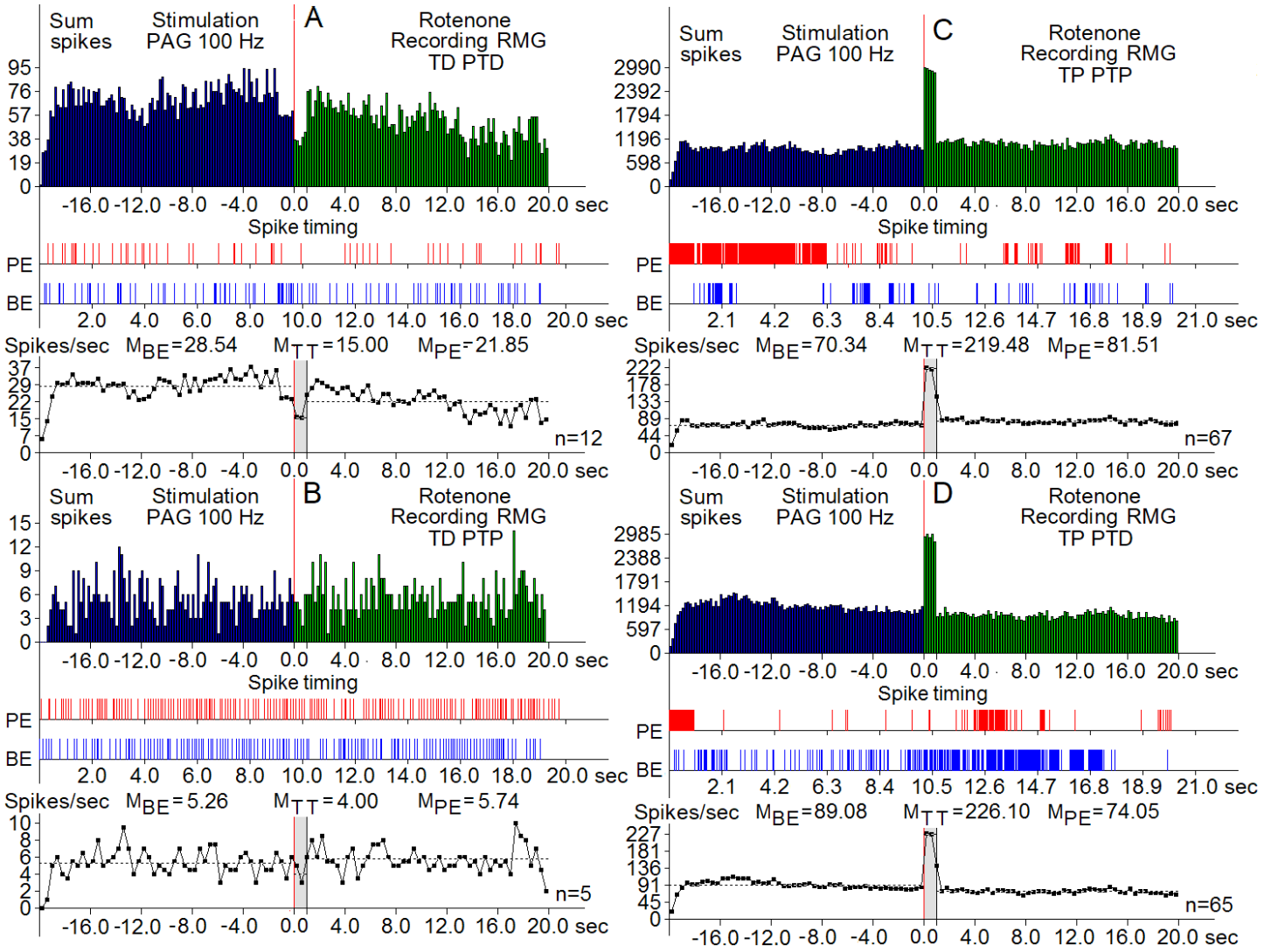
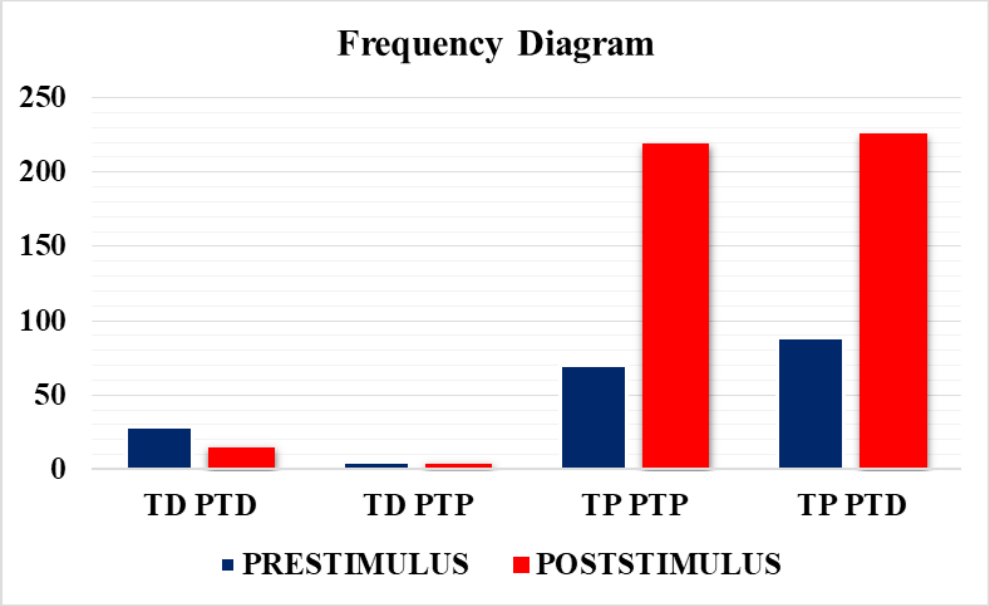


Figure 2: A-D – histograms of sum spikes pre- and post-stimulus tetanic depressor manifestations of activity (tetanic depression post tetanic depression - TD PTD) (A), in conjunction of with post tetanic excitatory (tetanic depression post tetanic potentiation - TD PTP) (B), excitatory (tetanic potentiation post tetanic potentiation) (C), in conjunction with the post tetanic depressor (tetanic potentiation pops tetanic depression – TP PTD) (D) neurons of RMG, evoked at PAG HFS on the model of PD, in real time 20 sec (before and after stimulation). The raster of activity on A-D – detailed analysis of arbitrarily chosen single neurons from this group. Diagrams frequency of spikes, presented in histograms, with averaged values (M) for time periods prior to (BE - before event), at the time of tetanization (TT - time tetanization) and after stimulation (PE - post even). To the right of the diagrams – number of tests (n). The remaining symbols are in the Figure.

The prestimulus frequency of RMG neurons activity at PAG HFS on the model of PD, prior to depressor and depressor-excitatory sequences order 28.54 and 5.26, values reached, unlike in the excitatory and excitatory-depressor sequences – order 70.34 and 89.08, respectively (Figure 3), that indicates a significant prevalence of original (prestimulus) frequency activity of RMG neurons, responding by excitatory effects at PAG HFS in uni- and multidirectional sequences, respectively (order 2.46- and 17.0-multiple).

As regards the post stimulus frequency of RMG neurons activity at PAG HFS, accompanied by marked depressor and excitatory sequences, the ratio was calculated within 15.0 and 4.0 for uni- and multidirectional depressor sequences and order 219.48 and 226.1 – for corresponding excitatory. In other words, the difference turned out to be even higher – order 14.6 and even 56.5-multiple for uni- and multidirectional poststimulus depressor and excitatory sequences, accordingly. Besides, especially above-for multidirectional.

Thus, on the model of PD in RMG neurons the powerful excitotoxicity has been revealed, testifying about serious neurodegenerative defeat the important ant nociceptive structure, promotes the emergence of resistant chronic pain. As a result of over activation of NMDA and AMPA glutamate receptors, accompanied by a number of negative effects in the form of violations of calcium buffering, the generation of free radicals, activation of mitochondrial permeability [43], that indicates a



	TD PTD	TD PTP	TP PTP	TP PTD
PRESTIMULUS	28,54	5,26	70,34	89,08
POSTSTIMULUS	15	4	219,48	226,1

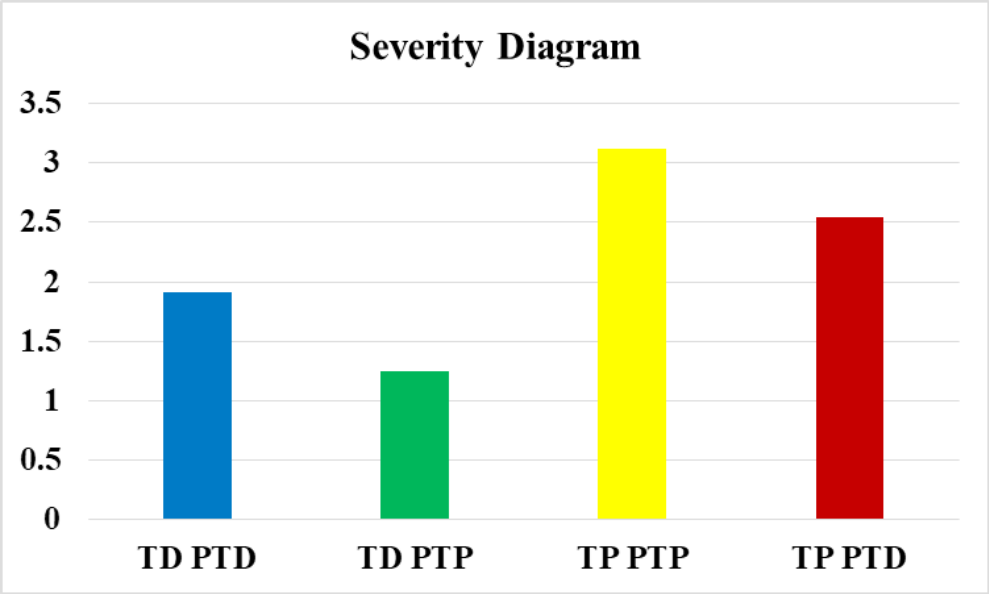


Figure 3: Degree of evidence (on average frequency) of depressor (tetanic depression posttetanic depression - TD PTD), depressor-excitatory, (tetanic depression posttetanic potentiation - TD PTP), excitatory (tetanic potentiation posttetanic potentiation - TP PTP) and excitatory-depressor (tetanic potentiation posttetanic depression - TP PTD) poststimulus effects in single neurons of RMG at HFS PAG on the rotenone model of PD. Designations: degree eviden. – degree evidence, Prestimul. - Prestimulus, Poststimul. – Poststimulus.

profound neurodegenerative defeat of important ant nociceptive structure RMG, promotes the emergence of resistant chronic pain. There is an obvious need for deepening depressor effects protector destination and reduce excessive excitatory [44].

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