

Adrenergic Alpha-2 Receptor Antagonists Regulate Noise-induced Metabolic and Cognitive Changes in Rats

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Abstract

Background: Noise is a modern life wide-spread stressor produced by urban traffic and the industrial environment. The noise stress causes central nervous system's dysfunction and neurotransmission impairment in the brain, as well as changes the hormones levels resulting in psychological and behavioral problems. Underscoring the chronic stress implications, this investigation was to study the level of inositol triphosphate (IP₃) in the mitochondrial fraction of the brain (MFB), and α -Tocopherol (α -T) and malondialdehyde (MDA) in the plasma and erythrocytes' membrane (EM). At the same time, the behavioral characteristics of experimental animals, and the influence of α_2 -adrenoblockers to evident their modulating effect during noise exposure were studied.

Results: The obtained results imply increase of plasma and erythrocytes' membrane MDA content and decrease in IP₃ and α -T and impacted cognitive functions.

Conclusion: The use of α_2 -adrenoblockers to the noise-exposed animals by the specific tests revealed a regulatory effect on the noise time-dependent delay in behavioral activity manifested by disorientation, and the spatial memory deficit. Reduction of the noise impact by α_2 -adrenoblockers was expressed by less level of MDA and increased level of IP₃ and α -T in the plasma and EM, in the 3rd and the 4th groups.

Background

Noise is an unwanted product of urbanization becoming increasingly dangerous for humans and animals [1]. It may affect patient's health both at auditory and non-auditory levels, although it has been largely proved to be a common cause of hearing loss, and one of the most common causes of stress [2]. Noise-induced stress promotes enhancement of the free oxygen radical's intensity through the metabolic turnover. In this respect MDA is important in the oxidative stress assessment and serves as a marker of LPO-mediated damage in tissues [3,4,5]. These pathological states development is associated with free-radical oxidation intensification [6,7], finally resulting in functional disturbances in tissues. That is why the antioxidants are crucial in stress conditions [6]. Reportedly, some data are controversial [8]. Notably, the reactive antioxidants can be stabilized by other antioxidants, which in turn become reactive and can be recycled in a cascade of reactivity as a matter of equilibrium [9]. Evidently, oxidative stress is a result of imbalance favoring the oxidants [10] termed by Dündar as "antioxidative stress" [11].

Noteworthy, that use of adrenoblockers evokes a definite regulating effect on oxidative processes under the stress conditions [12]. As the noise-induced metabolic changes are the case of stress response the adrenergic signaling system, particularly of α_2 -adrenoreceptors, become an object of our investigation. In a search of new alternatives for α_2 -adrenergic blockers, 1,4-benzodioxane derivatives have been identified as potent selective α_2 -adrenoblockers. These compounds, mesedin and beditin have been chosen for the further studies as the α_2 -adrenoreceptors blockers. It was preferable because of their less harmful effect compared with idazoxan [13].

An urban noise is a type of the potent stressor [14]. On the other hand, as the hippocampus (HIP) was found to be an important target for stress [15], the noise can produce long-term impact on the cognitive function at early stages of stress. At the same time, the noradrenergic system's participation in anxiety development is well documented [16], but the specific role of α_2 -adrenoreceptors in anxiety is still to be clarified.

Y maze is used to study cognitive impairment in animals. The test is also broadly used to estimate spatial memory and exploratory behavior enabling measurement of both quality and quantity of the activity [17]. That is why the stress reaction itself is one of the most important elements which impair the cognitive response [18].

Thus, the objectives of this study included revealing of a possible dependence between the oxidation intensity by determining the level of MDA and α -T in plasma and EM, the cognitive changes in rats under the noise exposure and influence of beditin and mesedin on them. Taking into account the important regulatory function of phosphoinositids (PI) in the signaling system and ensuring membrane functions, we studied the content of IP_3 as a minor fraction of membrane phospholipids (PL) in the experimental animals' brain mitochondria. The present study also included a comparison of these substances' capability in regulation of the metabolic changes with determination of the most effective one under the given conditions.

Methods

The aim of our investigation was to study the level of the MDA and α -T in the plasma and EM, the level of IP_3 in MFB, as well as the behavioral characteristics of experimental animals, and the beditin and mesedin α_2 -adrenoblockers influence to evident their modulating effect during noise exposure.

Animals

Investigations have been carried out on albino, male rats [19,20] weighing 150-200g (aged 5-6 weeks), kept in ordinary vivarium conditions, maintained on a 12 h light/dark cycle with food and water and libitum in accordance with the European Communities Council Directive (86/609/EEC) on care and use of animals for experimental procedures. All applicable institutional guidelines for the care and use of animals were followed. The protocol was approved by the Institutional Animal Care and Ethics Committee. The following specific *in vivo* conditions were kept for each experiment: 20⁰C temperature and 52% humidity. The animals were accommodated to the laboratory conditions for 7 days prior to the experiment. The rats were grouped into 4 groups (6 per group). The 1st group was a control; the 2nd group (noise) was just exposed to noise, the 3rd (beditin - (2-amino-4-thiozoly) -1,4-benzodioxan)) and 4th (mesedin -(2-(2-methylamino-4-thiozoly) -1,4-benzodioxan hydrochloride)) groups - to 91 dBA white noise with the maximal energy in the regions of average and high frequency. The duration of noise effect was 7, 30 and 60 days [21] with an 8 h window of noise exposure daily; animals of the 3rd and 4th groups were

injected with beditin (2mg/kg) and mesedin (10mg/kg) intraperitoneally, correspondingly. The first injection was carried out 12 h prior to the exposure. Injections were repeatedly done each 24 h.

Noise Exposure Setup

During noise exposure, rats were housed one per cage to avoid shielding each other from the noise. Therefore, noise-exposed rats (n = 18) were individually placed for 8 hours in cages close to loudspeakers (12 W) mounted, 40 cm apart, on opposite sides of the cage and activated by a white-noise generator (10-20 kHz) of a frequency range of 10000-16000Hz. The noise level was set at 91dBA (60 consecutive days, 8 h per day, from 1:00 to 9:00) [20] and was uniform inside the cage, as monitored with a sound meter (ST 11 D).

Protein carbonyl content assay

Determination of MDA

The MDA level in plasma and erythrocytes membrane were measured by Esterbauer and Cheeseman method [21] based on its reaction with thiobarbituric acid (TBA) at 90–100°C and measurement of the absorbance at 532 nm. MDA reacts with TBA and produces a pink pigment which has maximum absorption at 532 nm. The value of each sample was obtained from the standard curve and expressed as nmol/mL.

Determination of α -T content in blood plasma and EM

α -T in erythrocyte membranes and blood plasma was determined by the Duggan fluorometric method [22] at an excitation maximum of 295 nm and a fluorescence maximum of 330 nm. 0.75 ml of blood plasma, or 1.5 ml of a suspension of erythrocyte membranes, or the mitochondrial fraction of the brain, was poured into a test tube with a thin section of 15 ml, 1.25 ml of bidistilled water was added in the case of plasma or 0.5 ml in the case of erythrocyte membranes and the mitochondrial fraction of the brain, and 3 ml of absolute alcohol. Then everything was thoroughly mixed, and 6 ml of hexane was added; the tubes were closed with stoppers and thoroughly shaken for 10 minutes. After separation in the hexane phase, α -T was determined. To determine α -T 1 ml, the hexane phase was mixed with 3 ml of absolute alcohol; the sample was subjected to fluorimetry at 295/330 nm. The amount of α -T was calculated from a standard calibration curve and expressed in μ mol per dl of plasma and in μ g per mg of erythrocyte membrane protein.

Determination of IP₃ content

a) Extraction of phospholipids of the mitochondrial fraction of the brain

To determine PL, it was extracted from the mitochondrial fraction of the rat brain using the Bligh and Dyer method modified by Kargapolov [23]. For this purpose, 2-3 ml of a mixture containing chloroform and methanol in a ratio of 1: 2 was added to the samples and filtered. The precipitate formed on the filter was

washed three times with a chloroform-methanol mixture (2:1) and once with warm methanol. 2-3 ml of 0.2% CaCl₂ solution was added to the filtrate and shaken for 2 min, after which 2-3 ml of chloroform was added. The filtrate was centrifuged for 3-5 min at 3000 rpm, and then the surface water-methanol phase was isolated. The residue was washed once with 2 ml of chloroform solution to remove the remaining lipids. After centrifugation, chloroform extracts were added. The resulting extract was washed three times with a solution of chloroform-methanol-0.02% CaCl₂ (3:48:47) with centrifugation each time. By removing the surface water-methanol phase, a chloroform extract of phospholipids was obtained.

b) Acid extraction of phosphoinositides of the mitochondrial fraction of the brain

To obtain PI, the method of selective acid extraction was used [24]. To isolate PI, we used precipitates on the filter after PL extraction, to which a mixture of chloroform-methanol- HCl concentrated solution (2: 1: 0.01) was added. At the room temperature, shaking time to time, after incubation for 37 minutes the mixture was centrifuged for 5 min at 4000g. The extraction was repeated twice. After the third centrifugation, the supernatants were combined. The total extract was washed sequentially by: 1N HCl, then a mixture of 1N chloroform-methanol -1N HCl (3:48:47) and chloroform-methanol-0.01N HCl (3:48:47). After each single washing, the mixture was centrifuged for 5 min at 4000g. After centrifugation, the upper layer was removed, and methanol was added to the cloudy acidic extracts until the solution became clear, then the pH was adjusted to 4.9 using the NH₄OH concentrated solution.

Y-maze

Spontaneous alternation tests were conducted in a Y-shaped maze with three wooden arms at a 120° angle from each other. After introduction to the center of the maze, the animal was allowed to freely explore the three arms. Spontaneous alternation was defined as consecutive entries in 3 different arms (A, B, C), divided by the number of possible alternations [25]. An entry was considered when all four limbs were in the arm. Rats were group-housed in standard polycarbonate cages. Approximately 3 minutes before each assay, the animal was removed from its home cage and placed in a clean holding cage for transfer. Rats were placed in the center of the Y-maze and allowed to explore the apparatus for 5 minutes. Each trial was recorded for later analysis, using a video camcorder positioned 2.1m above the apparatus. After the 5-minute tests, the rats were taken back to their home cages and the Y-maze were cleaned with 70% ethyl alcohol and permitted to dry between tests. The numbers of entries to the A, B and C zones were compared within the groups.

Statistical analysis

The behavioral parameters have assessed with the help of Any-maze system, the video tracking system for the location and movement observing.

All analysis was performed using BIOSTA system. All measurements were represented as mean ± SEM. Significance of means' difference was evaluated using paired Student Newman – Keuls test (Anova).

Statistical significance, determined by one-way ANOVA, was set at $P < 0.05$ (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

Results

Level of MDA in plasma under the chronic acoustic stress conditions

The study of LPO processes intensity revealed statistically significant difference in MDA levels in plasma between the 4 groups (Table 1). Our results have shown drastically increased level of MDA in the 2nd group after 7, 30 and 60 days in the acoustic stress conditions ($t = -4,7$, $p < 0,001$; $t = -5,8$, $p < 0,05$; $t = -11,9$, $p < 0,001$ respectively), whereas the noise impact has been diminished by influence of α_2 -adrenoblockers, which is better expressed in low levels of MDA in the 3rd ($t = -0,03$, $p = 0,097$; $t = -3,16$, $p < 0,05$; $t = 0,18$, $p = 0,86$ respectively) and in the 4th ($t = 4,44$, $p < 0,01$; $t = -3,02$, $p < 0,05$; $t = 9,28$, $p < 0,001$ respectively) groups.

Level of MDA in EM under the chronic acoustic stress conditions

Our results have shown, the LPO intensity significantly increased in EM after 7, 30 and 60 days of noise exposure in the 2nd group ($t = -3,93$, $p < 0,01$; $t = -2,23$, $p < 0,05$; $t = -7$, $p < 0,001$, respectively) (Table 2). Administration of α_2 -adrenoblockers promoted to decrease in the level of MDA, which was noticeable in the 3rd ($t = 0,29$, $p = 0,77$; $t = 3,3$, $p < 0,01$; $t = 1,28$, $p = 0,22$ respectively) and in the 4th ($t = 1,78$, $p = 0,1$; $t = 3,73$, $p < 0,01$, $t = 0,57$, $p = 0,7$ respectively) groups after 7, 30 and 60 days of the chronic noise influence.

Content of α -T in plasma under the chronic acoustic stress conditions

Fig.1 shows the level of α -T in the plasma under the chronic acoustic stress conditions. Our results have shown oxidation significant intensification for the 2nd group after 7, 30 and 60 days in the chronic noise conditions. At the same time, this impact was reduced by influence of α_2 -adrenoblockers, expressed by low oxidation intensity levels of the plasma α -T in the 3rd and in the 4th study groups, comparably to the noise group.

Content of α -T in EM under the chronic acoustic stress conditions

Fig.2 shows the level of α -T in EM under the chronic acoustic stress conditions. The content of α -T in the rats of the 2nd group was less compared with the 1st, 3rd and 4th groups. It was shown that 7 days introduction of adrenoblockers increased the level of α -T compared to the 2nd group. The improving effect of beditin and mesedin was continued after 30 and 60 days of the noise action, but the data of the 3rd and 4th group rats were less than in control.

Changes in the intensity of lipid peroxidation (IP_3) in the MFB under the chronic acoustic stress conditions

Analysis of peroxidation intensity of lipids revealed statistically significant shifts in IP_3 levels in MFB under the chronic noise influence (Table 3). Our results have shown decreased level of TPI in the 2nd group after 7, 30 and 60 days in the acoustic stress conditions ($t=10,5$, $p<0,001$; $t=9,6$, $p<0,001$; $t=-12,8$, $p<0,001$, respectively). The noise effect has been decreased by influence of α_2 -adrenoblockers, which was noticeable in higher levels of TPI in the 3rd ($t=3,5$, $p<0,01$; $t=2,6$, $p<0,05$; $t=2,4$, $p<0,05$, respectively) and the 4th groups ($t=2,5$, $p<0,05$; $t=1,8$, $p=0,1$; $t=0,45$, $p=0,66$, respectively). Moreover, the data of IP_3 in the 4th group rats were close to control after 60 days of exposure.

Number of entries and alternations of animals to the arms of A, B, C

Fig. 3,4,5 show a number of entries and alternations of animals to the arms of A, B, C. under the acoustic stress conditions after 7, 30 and 60 days. Our data have shown that the rats of the 2nd group had a smaller number of entries and alternations to the A, B, C arms compared with the 1st, 3rd and 4th groups after 7, 30 and 60 days of exposure. The data of the 4th group for the 7, 30 and the 60 days of exposure were higher than the control. The rats of the 3rd group had less number of entries to the A zone, while that for the 30 and 60 days of exposure were close to control. But the number of entries to the B zone after 7, 30 and 60 days of exposure higher than control. The data of the 3rd group number of entries to the C zone less for the 7 day of exposure compared to control, while that for the 30 and 60 days of exposure were higher than control.

Discussion

Based on the revealed data the chronic noise action increased the level of peroxidation of membranes phospholipids in MFB and the level of MDA and decreased content of α -T in the plasma and EM of experimental animals. The Y-maze test also revealed cognitive disorders in rats under the noise action. The results obtained indicate onto changes in the studied biochemical parameters and the cognitive function, so testify about the regulative effects of the α_2 -adrenoblockers under the conditions of the chronic noise.

The stress realization phenomenon is a nonspecific response of the central nervous system (CNS) to a stressor with several morphological and biochemical deviations including those characteristics to the oxidative stress.

The processes of free radicals' production dysregulation led to oxidation intensity changes consistent with a shift in MDA level, one of the most common biomarkers of LPO. The enhanced level of MDA also indicates on abnormality in antioxidant defense mechanisms. Results of our investigations have shown that chronic noise increased level of MDA in the plasma of the 2nd group, which is an accepted marker for oxidative stress and development of pathology [3]. Meanwhile, we recorded the noticeable restorative effects of beditin and mesedin on the levels of MDA in respective groups. Low levels of MDA in plasma of these groups were caused by the α_2 -adrenoblockers, where effect of mesedin was the mostly

expressed. The latter was evident by the 4th group rats' lowest MDA level, compared with the 1st group after 7 and 60 days of noise action.

Based on the data in the plasma levels of MDA, we found significant difference after noise exposition. Indicators of oxidative stress can be detected in various body fluids or tissues [26]. MDA is a product of lipid peroxidation, which immediately reacts with biomolecules in the cells [27]. Its increase indicates intensified oxidative stress in erythrocytes membranes due to an excessive production of ROS by noise action.

Our data demonstrated expressed quantitative deviations of MDA level in the EM under the noise exposure in the 2nd group. Interestingly, the stress-realizing hormones action brings to structural transitions in EM proteins, along which the deformation of erythrocytes is [28]. Structural changes of EM can promote oxidation of proteins and phospholipids by becoming a target of ROS. It was also shown that stress hormones alter the oxygen transport properties of erythrocytes. Increased level of MDA followed by development of oxidative stress could be one of the pathophysiologic mechanisms of diseases [29].

As a protective measure we used α_2 -adrenoblockers, mesedin and beditin, to reduce noise-induced symptoms and show their possible preventive effect under the chronic acoustic stress conditions. Reduction of the noise impact by α_2 -adrenoblockers was expressed by less level of MDA in the EM, in the 3rd and the 4th groups. Low level of MDA in these groups was caused by regulatory properties of α_2 -adrenoblockers [12, 30] compared with the 1st group after 7, 30 and 60 days of noise exposure.

The cellular effects of oxidative stress are characterized by free radicals, including ROS, which affect the molecular components of the cell membrane spatially membrane lipids and disturb their biophysical properties. In this aspects α -T is of widely recognized antioxidant action and as a lipid-soluble molecule, scavenging its free radical in the cell membranes and protecting primarily poly unsaturated fatty acids (PUFA), highly susceptible to oxidative attack [31,32].

In the given study in the 2nd rats α -T level was reduced in the EM and plasma after 7 day of noise influence, compared to control. The oxidative damage was continued by chronic exposure of noise (after 30 and 60 day), which was expressed by intensive decreased level of α -tocopherol in the 2nd group rats. Based on our data, we can postulate, that harmful effect of noise decreased endogenous antioxidant defense because of gradually decreasing scavenging of the free radicals and thus, damaging the cells. In the antioxidant defense overwhelming the oxidative stress to the cellular components induce adaptive processes [33]. The data from our previous study also confirmed this fact and showed adaptation processes on the 30th day of the noise exposure. However, α -T studies have shown that noise-induced reductions in tocopherol levels were not accompanied by the adaptation phase. The amount of tocopherol was gradually decreased bypassing adaptation. A study of the effects of beditine and mesedin showed that oxidative stress was limited by using of these α_2 -adrenoblockers, which was expressed by a slight increase of α -T in the studied group, compared to the noise group. Contributing to

α -T levels, α_2 -adrenoblockers protected PUFA in cell membranes from LPO and preserve the physical properties of the membranes [34]. Considering the biological effects specificity inhibited by α -T, it does not seem plausible that numerous effects can be mediated by uncontrolled LPO and so, counteracted by the antioxidant [35]. By protection of the structure of PUFA, α -T is considered to significantly influence the physical properties of the cell membrane.

To date, researchers' attention is focused on IP_3 , as minor components of the cell membranes, which play both a structural and a signaling role. Disorders of IP_3 metabolism in such pathologies as cancer, cardiovascular diseases, and the immune system dysfunctions, where the acoustic stress is of importance, are the red-ox and the IP_3 metabolism imbalance result [36]. IP_3 are the precursors of several secondary messengers of various intracellular signaling pathways.

The study of quantitative shifts in the fraction of IP_3 of brain mitochondria under the conditions of acoustic stress revealed a decrease in the content of IP_3 in the 2nd group compared to other experimental groups, after 7, 30 and 60 days of noise exposure.

Disorders of the metabolism of IP_3 , associated with the activation of free radical processes have been described in some diseases [37]. The study of quantitative changes in the fraction of IP_3 of brain mitochondria under the conditions of chronic acoustic stress revealed a decrease in the content of IP_3 . As a result, the development of disorders in phosphorylation / dephosphorylation of the inositol ring, responsible for the implementation of regulatory mechanisms of the functional activity of membrane surface proteins and signaling complexes occur [37]. IP_3 is also involved in such cellular processes, as cell growth, differentiation and survival, and the signaling regulation. Based on the results of our research, we can state that the impact of noise disrupts the above-mentioned processes leading to pathological events. However, intraperitoneal administration of beditin and mesedin during exposure to noise has a regulatory effect on the content of IP_3 after 7, 30 and 60 days of noise action. [Adrenergic alpha-2 receptor antagonists](#) exhibit the antioxidant properties and thereby prevents the lipid peroxidation intensification by maintaining the level of α -tocopherol in blood plasma and EM within physiological ranges when exposed to noise. Notably, mesedin did not cause significant changes in the studied parameters in relation to the control group, implying its higher efficacy.

Results of our previous investigations have shown that chronic noise impact increased carbonylation of FG and EM proteins [38] which also are known markers for oxidative stress, mediating redox signaling processes and development of pathology.

Considering the given study results of the α_2 adrenoblockers influence on the above-mentioned processes, we can conclude that mesedin and beditin possess significant regulating properties judging by the MDA level dramatically decrease. In the given study, where mesedin was of a special significance in this regard, this effect might be probably mediated by decrease intensiveness of ROS formation and, as a result, the MDA level reduction.

Adrenaline and noradrenaline catecholamines' effects, namely their radical scavenging activity, can be efficient for reducing oxidative stress though a loss of their activity was also mentioned [8]. Consequently, regarding oxidative stress they can be both protectors and molecular targets. It should be also noticed, under the proper conditions both catecholamines can be regenerated to their original form so their functions can be restored [39]. So, according to our previous data, one of the main advantages of α_2 -adrenoblocker action is its regulatory effect on lipoprotein metabolism [38]. Environmental noise has its stress-realizing effects through the direct connections to the neural mechanisms via the autonomic nervous system [40], and different mediated connections to the cerebral centers responsible for the principal physiological and behavioral effects of organism [41]. It is well-known, that the major physiological effect of α_2 -adrenoceptors is to block the presynaptic feedback of neurotransmitter release from noradrenergic terminals [42].

Exposure of laboratory animals to noise induced abnormal behavior, suppressed exploratory attempts and impaired memory, but some forms of chronic stress could also produce depressive-like symptoms, like anxiety [38]. The HIP is an important structure of the CNS involved in the cognitive processes' realization, so in the pathogenesis of mood and anxiety disorders through its dorsoventral axis [43]. Recent data of some studies evident that manipulation of the vHIP itself can directly impact anxiety-related behavior [44].

The CNS peculiarities include high sensitivity to LPO due to high oxygen supply and rich content of polyunsaturated fatty acid. According to Marchasson et al., in Alzheimer's disease the MDA levels found higher in the patients' plasma [26]. The fact, that the hippocampus is affected by noise, is well documented [15,17]. Many pathological processes, such as post-traumatic stress disorders involve HIP as the primary damage site. Changes in the neurotransmitters contents in the brain are associated with degenerative disease of CNS, brain injury and cognitive disorders [45].

For new environment accommodation in Y-maze the rats generally prefer to enter a new arm of the maze more often rather than returning one that was previously visited. The Y-maze test is a specific behavioral test for the memory and the animal's behavior alternation assessment. The Y-maze test's results presented in this research confirmed the harmful impact of chronic noise exposure on the animals' spatial memory. By counting alternations sequences it was shown many incorrect alternations in the noise group. Correct alternations were BAC, CBA or ACB, etc., but in the noise group there was predominant incorrect alternations. Moreover, there was also noticed a high-level immobility in the noise group animals resulting to less distance travelled during alternation sequences, hence, the less number of entries to the different arms. This phenomenon can be explained by a deteriorating effect of noise on the organism leading to a memory weakness, and as a result, to wrong alternations.

Evidentially, the noise-induced stress led to a spatial memory deficit, which in turn brought to the orientation impairment. Observing this parameter change we recorded the exact opposite pattern in the mesedin and beditin rats' groups. These α_2 -adrenobloskers decreased noise-induced stress and thus, restored anxiety-induced spatial memory.

With the OFT study our previously results had shown increased anxiety level induced by noise [39]. The increased levels of anxiety were accompanied by the immobility and disturbance orientation of rats. So, the noise-associated psycho-emotional stress is capable to mitigate anxiety-related behavior by driving a release of norepinephrine in the neuronal system of organism. Results of our study demonstrated the behavioral changes in the Y-maze tests after the α_2 -adrenoblockers injection, consisting in ceasing of the stress-induced immobility of rats after 60 days of chronic noise action. The anxiolytic action of α_2 -adrenoblockers in rats administered mesedin and beditin was expressed by reduced anxiety and increased total locomotor function.

Conclusion

The study results provide evidence increased the level of MDA in plasma and erythrocytes' membrane of animals subjected to the chronic noise action. The latter developed imbalance in the redox status, favoring oxidation of proteins and phospholipids and generating ROS. MDA measurement is very important in different pathological states, and it has also a great significance in the effects of many pollutants, particularly in environmental noise action. Moreover, environmental noise ameliorated conditions causing a noise duration-dependent deficit in spatial memory in rats and regulatory mechanisms of the functional activity of membrane surface proteins and signaling complexes. We can conclude that α_2 -adrenoblockers, mesedin and beditin, provided a modulatory effect on the investigated values under the chronic acoustic stress, which was mostly expressed by mesedin. Summarizing our data, it can be suggested, that the adrenergic alpha-2 receptor antagonists exhibit the antioxidant properties that prevents the intensification of LPO, while maintaining the level of α -tocopherol in blood plasma and EM and the IP_3 content in the brain mitochondria under the chronic noise conditions.

Declarations

Ethics approval and consent to participate

All applicable institutional guidelines for the care and use of animals were followed. The protocol was approved by the Institutional Animal Care and Ethics Committee.

Consent for publication

Not applicable

Availability of data and material.

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Content of MDA in plasma under the acoustic stress conditions after 7, 30 and 60 days.

Groups	7X8	30X8	60X8
Control	0,17±0,003	0,17±0,003	0,17±0,003
Noise	0,23±0,01***	0,24±0,011*	0,23±0,01***
Noise + Beditin	0,17±0,004	0,2±0,003*	0,17±0,004
Noise + Mesedin	0,14±0,005**	0,19±0,006*	0,14±0,005***

The statistical difference is provided between control and experimental groups

*(*P < .05, **P < .01, ***P < .001)*

Table 2. Content of MDA in EM under the acoustic stress conditions after 7, 30 and 60 days.

Groups	7X8	30X8	60X8
Control	2,26±0,03	2,26±0,03	2,26±0,03
Noise	3,13±0,22**	2,6±0,014*	3,22±0,1***
Noise + Beditin	2,19±0,22	1,89±0,1**	2,08±0,1
Noise + Mesedin	2,07±0,1	1,8±0,11**	2,13±0,21

The statistical difference is provided between control and experimental groups

*(*P < .05, **P < .01, ***P < .001)*

Table 3. Content of inositol triphosphate in the of mitochondrial fraction of brain under the chronic noise conditions after 7, 30 and 60 days.

Groups	7X8	30X8	60X8
Control	46±1,61	46±1,61	46±1,61
Noise	23±1,46***	26±1,31***	19±1,3***
Noise + Beditin	37±1,94**	40±1,67*	41±1,5*
Noise + Mesedin	40±1,77*	42±1,5	45±1,52

The statistical difference is provided between control and experimental groups

(*P < .05, **P < .01, ***P < .001)

Figures

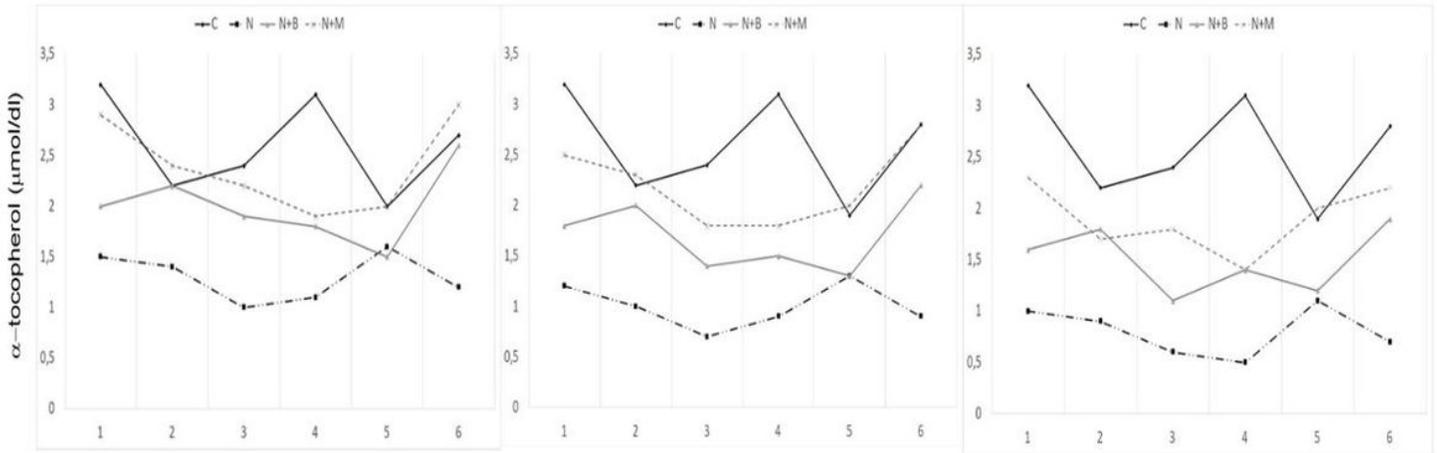


Figure 1

Content of α -T in plasma under the chronic acoustic stress conditions (each group is of 6 animals, under the 8hr noise /day action). According to the data after 7(I), 30(II) and 60 (III) days of noise action the 2nd group rats have had increased level of oxidative intensity ($p < 0,001$, $p < 0,001$, $p < 0,001$, respectively) compared with the 1st group. The 3rd ($p < 0,5$, $p < 0,01$, $p < 0,001$, respectively) and the 4th ($p = 0,48$, $p = 0,15$, $p < 0,01$, respectively) groups have had low oxidation intensity, compared to the 2nd group. However, the data of the 3rd and the 4th groups level in the plasma of α -T were less than of control.

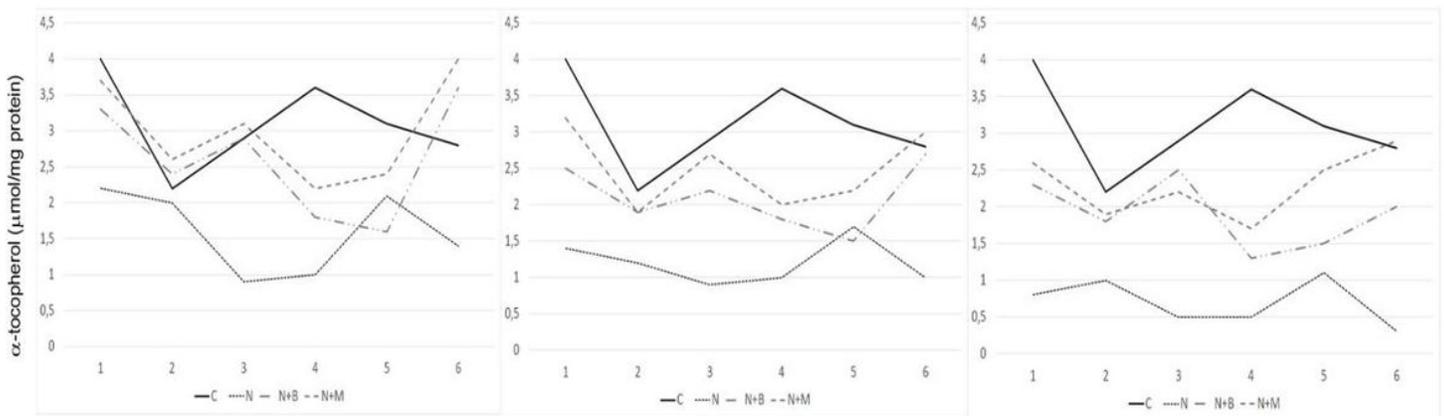


Figure 2

Content of α -T in EM under the chronic acoustic stress conditions (each group is of 6 animals, under the 8hr noise /day action). According to the data after 7 (I), 30 (II) and 60 (III) days of noise action the 2nd group rats have had increased level of oxidative intensity ($p < 0,01$, $p < 0,001$, $p < 0,001$, respectively) compared with the 1st group. The 3rd ($p = 0,22$, $p < 0,05$, $p < 0,01$, respectively) and the 4th ($p = 0,8$, $p = 0,1$, $p < 0,05$, respectively) groups have had low oxidation intensity, compare to the 2nd group. However, the data of the 3rd and the 4th groups level of α -T in EM less than control.

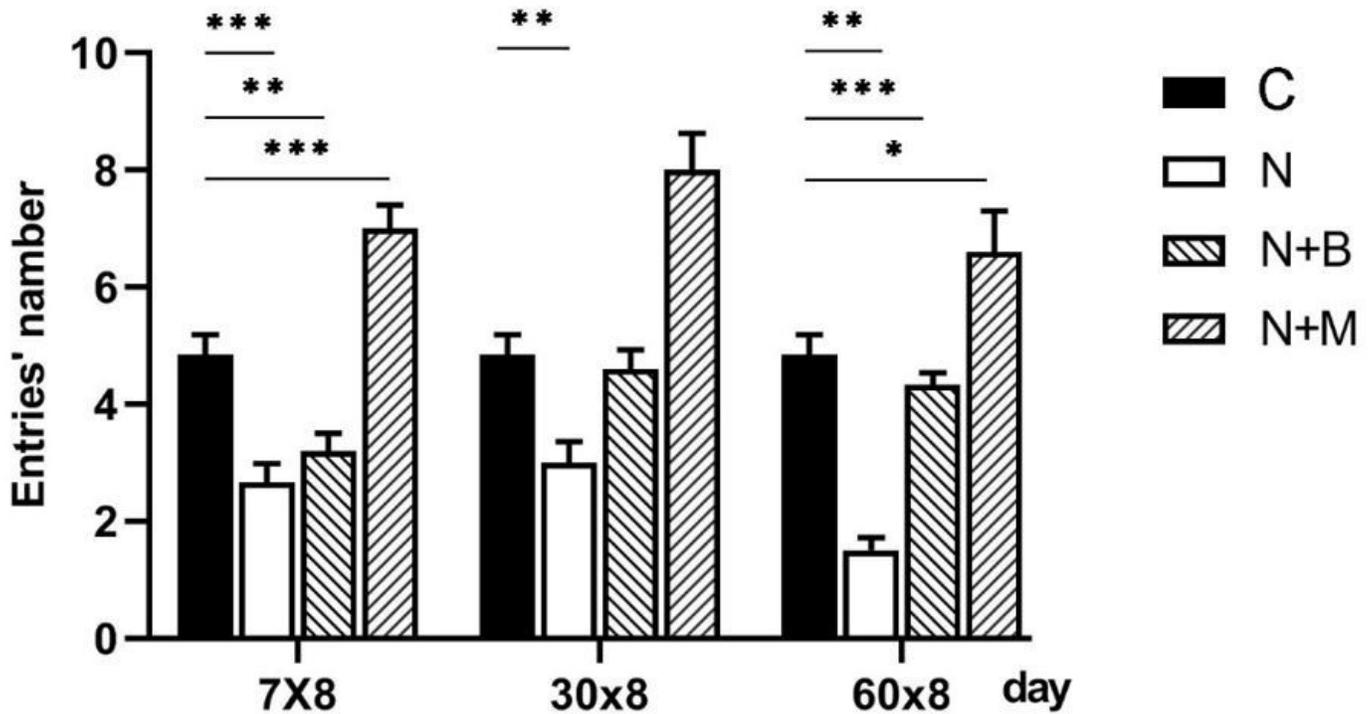


Figure 3

Number of entries to the A zone (each group is of 6 animals, under the 8hr noise /day action). According to the data after 7, 30 and 60 days of noise action the rats of the 2nd group have had 54,8%, 61,8%, 30,9% number of entries to the A zone compared with the 1st group (was as 100%), respectively; the rats of the 3rd group have had 66%, 94,8%, 89,1%, respectively; and the rats of the 4th group have had 144,3%, 164,9%, 136%, respectively.

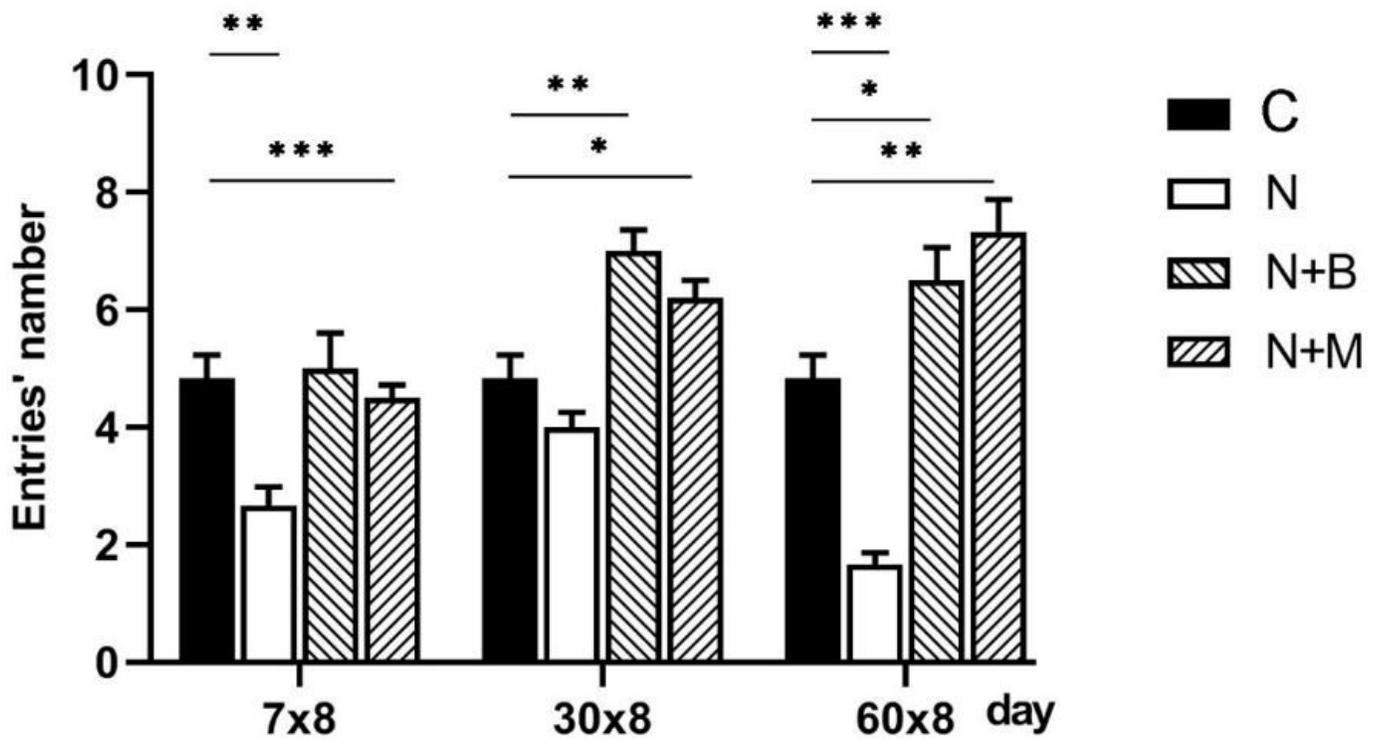


Figure 4

Number of entries to the B zone (each group is of 6 animals, under the 8hr noise /day action). According to the data after 7, 30 and 60 days of noise action the rats of the 2nd group have had 55%, 82,8%, 34,3% number of entries to the B zone compared with the 1st group (considered to be as 100%), respectively; the rats of the 3rd group have had 103,5%, 144,9%, 134,5%, respectively; and the rats of the 4th group have had 93,2%, 128,3%, 151,7%, respectively.

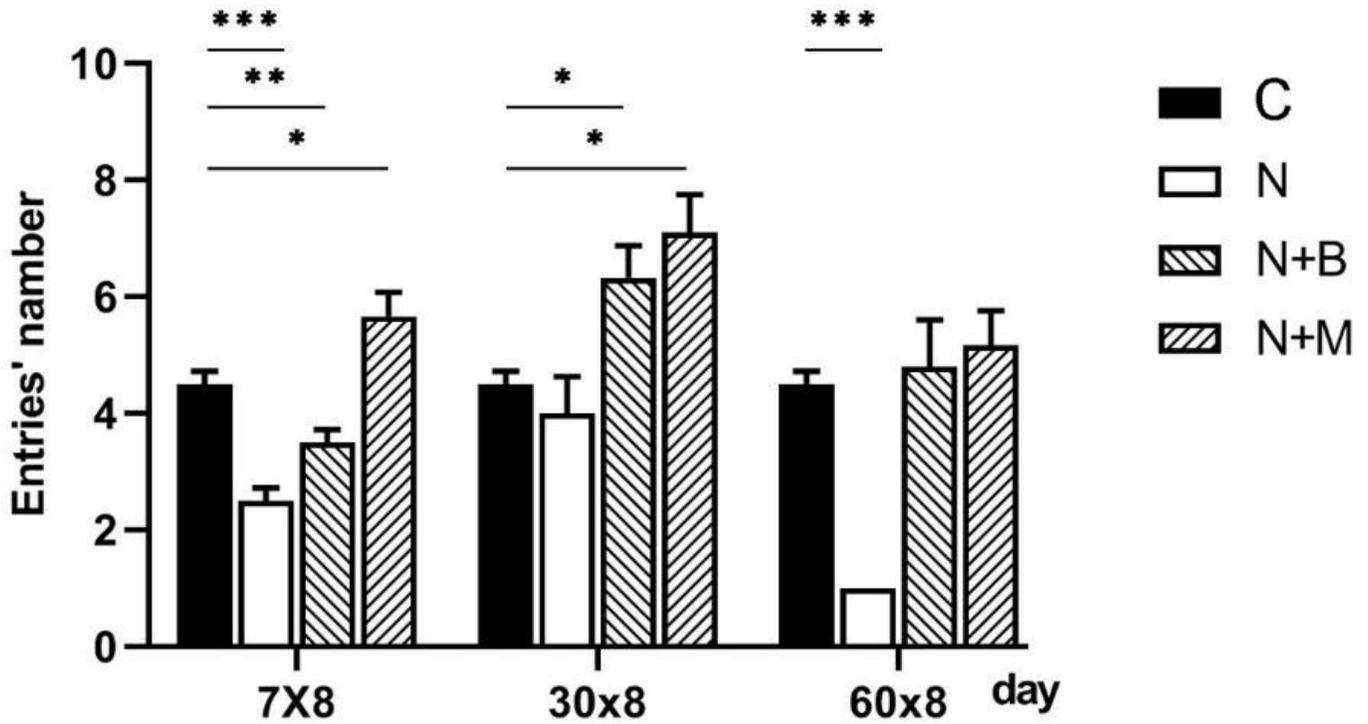


Figure 5

Number of entries to the C zone (each group is of 6 animals, under the 8hr noise /day action). As per the data after 7, 30 and 60 days of noise action the rats of the 2nd group have had 55,6%, 88,9%, 22,3% number of entries to the C zone compared with the 1st group (considered to be as 100%), respectively; the rats of the 3rd group have had 77,8%, 140,7%, 106,7%, respectively; and the rats of the 4th group have had 125,8%, 157,8%, 114,7%, respectively.