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 which potentially result in psychological and behavioral problems. Underscoring the implications of the chronic stress, the aim of our investigation was to study the level of the malondialdehyde (MDA) in the plasma and erythrocytes' membrane (EM), as well as the behavioral characteristics of experimental animals, and the influences of the α_2 -adrenoblockers to evident their modulating effect during noise exposure.

Results: The obtained results imply increase of plasma and erythrocytes' membrane MDA content which is an indicator of oxidative stress development. At the same time the noise impact decreases 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, increased anxiety, the spatial memory deficit. 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.

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, anxiety, and sleep disturbances [2]. Noise-induced stress promotes enhancement of the free oxygen radical's intensity through the metabolic turnover. In this respect MDA as an end product of ROS [3] is important in the process of oxidative stress assessment and serves as a marker of LPO-mediated damage in tissues [4, 5]. That is why the antioxidants are highly used substances in stress conditions [6].

At the same time some data are controversial [7]. It is known that 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 [8]. Evidently, oxidative stress is a result of the imbalance between reactive species and antioxidants, favoring the oxidants. Nevertheless, the equilibrium can be disturbed also when antioxidants prevail over the reactive species [9]. Dündar proposed the term "antioxidative stress" for this type of imbalance [10].

Noteworthy, that use of adrenoblockers evokes a definite regulating effect on oxidative processes under the stress conditions [11]. As the noise-induced metabolic changes are the particular 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 of five-membered heterocycle 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 [12].

An urban noise is a type of the potent stressor [13]. On the other hand, as the hippocampus (HIP) was found to be an important target for stress [14], 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 [15], but the specific role of α_2 -adrenoreceptors in anxiety is still to be clarified.

Appropriate behavioral tests (Y maze and open field) are used to study cognitive impairment in animals. The test is also broadly used to estimate anxiety, spatial memory and exploratory behavior enabling measurement of both quality and quantity of the activity [16]. That is why the stress reaction itself is one of the most important elements which impair the cognitive response [17].

Thus, the objectives of this study included revealing of a possible dependence between the oxidation intensity by determining the level of MDA in plasma and erythrocytes' membrane, the cognitive changes in rats under the noise exposure and influence of beditin and mesedin on them. The present study also included a comparison of these substances' possibility 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 in the plasma and erythrocytes' membrane, as well as the behavioral characteristics of experimental animals, and the influences of the α_2 -adrenoblockers beditin and mesedin to evident their modulating effect during noise exposure.

Animals

Investigations have been carried out on albino, male rats [18, 19] weighing 150–200 g (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: 20°C 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 [20] with an 8 h window of noise exposure daily; animals of the 3rd and 4th groups were injected with beditin (2 mg/kg) and mesedin (10 mg/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 loud speakers (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) [19] and was uniform inside the cage, as monitored with a sound meter (ST 11 D).

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.

Open Field

An open field [22] is a wooden square-shaped plate (60 × 60) with the 20 cm high walls. The animals' behavior was evaluated within 5 minutes in the middle of the plate. The number of entries to the different zones and the average freezing score were compared within the groups.

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. Generally, rats typically prefer to investigate a new arm of the maze rather than returning to one that was previously visited (ANY-maze). Over the course of multiple arm entries, the animal should show a tendency to enter a less recently visited arm. Alternation was considered to be ABC, BCA, CAB, etc., in any order or overlapping occurrence; but not ABA or BBC, etc. [23]. The number of arm entries and the number of trials was recorded in order to calculate the percentage of alternation. An entry was considered when all four limbs were in the arm. The numbers of entries to the A, B and C zones were compared within the groups.

Procedure

Rats were group-housed in standard polycarbonate mouse 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 open field and allowed to explore the apparatus for 5 minutes. Each trial was recorded for later analysis, using a video camcorder positioned 2.1 m above the apparatus. After the 5-minute tests, the rats were taken back to their home cages and the open field and

the Y-maze were cleaned with 70% ethyl alcohol and permitted to dry between tests. During the 7th, 30th and 60th days of exposure, the open field tests were carried out on all the animals. 2 days following these tests in all three iterations, the Y-maze tests were carried out. After the experiments, the rats were carried back to their home cages.

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 α₂-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.

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

Groups	7 × 8	30 × 8	60 × 8
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***
<i>The statistical difference is provided between control and experimental groups</i>			
<i>(*P < .05, **P < .01, ***P < .001)</i>			

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.

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

Groups	7 × 8	30 × 8	60 × 8
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
<i>The statistical difference is provided between control and experimental groups</i>			
<i>(*P < .05, **P < .01, ***P < .001)</i>			

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

Figure 1,2,3 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.

Number Of Entries To The Periphery Zone

Figure 4 shows the number of entries to the periphery zone in the open field test under the acoustic stress conditions after 7, 30 and 60 days. Rats of the 2nd group have had higher number of entries to the periphery zone compared with the 1st, 3rd and 4th groups. The 3rd group rat's behavior is quite notable, because of their less number of entries to the periphery zone after 30 and 60 days' action of noise compared with the control, while that for the 7 days of exposure were close to control. The data of the 4th group rats for the 7, 30 and 60 days of exposure were less than the control.

Average Freezing Score

Figure 5 shows the average freezing score in the open field test under the acoustic stress conditions after 7, 30 and 60 days. The average freezing score of the 2nd group rats was higher than the 1st, 3rd and the 4th groups rats after 7, 30 and 60 days of noise action. The data of the 3rd and the 4th groups average freezing score were higher compare to control for the 7 day exposure, while that for the 30 and 60 days of exposure were less than control.

Discussion

Based on the revealed data the chronic noise action increased the MDA levels in the plasma and EM of experimental animals. The open field test also revealed decreased locomotor and behavioral activity in rats under the noise action. The results obtained indicate onto changes in the studied biochemical parameters and also 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 a number of morphological and biochemical deviations including those characteristic to the oxidative stress.

The processes of free radicals' production dysregulation lead 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 was 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 [24]. MDA is a product of lipid peroxidation, which immediately reacts with biomolecules in the cells [25]. 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 [26]. 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 [27].

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 [11, 28] compared with the 1st group after 7, 30 and 60 days of noise exposure.

Results of our previous investigations have shown that chronic noise impact increased carbonylation of FG, plasma and EM proteins [29] 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 [7]. 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 [30]. So, according to our previous data, one of the main advantages of α_2 -adrenoblocker action is its regulatory effect on lipoprotein metabolism [28]. Environmental noise has its stress-realizing effects through the direct connections to the neural mechanisms via the autonomic nervous system [31], and also different mediated connections to the cerebral centers responsible for the principal physiological and behavioral effects of organism [32]. 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 [33].

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 [28]. Anxiety is a response to noxious stimuli and promotes adaptive avoidance behavior normally. 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, where the ventral HIP (vHIP) modulates emotional pattern [34]. Recent data of some studies evident that manipulation of the vHIP itself can directly impact anxiety-related behavior [35].

Our previous study data have shown down-regulation of the behavioral activity and more immobility in the 2nd group assessed by the number of entries to the central zone in the open field in chronic acoustic stress [36].

Our results clearly show the harmful effects of noise and the anxiolytic effects of α_2 -adrenoblockers by a number of entries to the periphery zone, as well. The rats in the OFT tried to stay close to protective walls instead of being exposed to danger in the open area [37]. The noise group rats' higher number of entries to the periphery zone and the less motility in it shows a high level of anxiety of the rats. Significant differences about number of entries to the periphery zone after 7, 30 and 60 days of noise action between the investigated groups demonstrated that the lesser number of entries to the periphery zone of the rats of 3rd and 4th groups was conditioned by the action of α_2 -adrenoblockers. Anyway, the effect of mesedin became more noticeable after 60 days of the noise impact and the positive manifestation of it was expressed by the lesser number of entries to the periphery zone of the 4th group rats. α_2 -adrenoblockers decreased a stress effect of the noise more and increased the rats' behavioral activity, correspondingly.

Our data showed behavioral and locomotor function impairment during the study of average freezing score. This parameter is consistent with the animals' immobility in the period of experiment noticing the scarce behavioral and locomotor activity [38]. There is a significance of the average freezing score on the behavioral and locomotor activity characteristic in the open field test. The high value of it testifies about the reduced behavioral and locomotor activity. Chronic noise decreased motility and increased anxiety of the noise group rats, which was expressed by higher number of average freezing score, than the rats of 3rd and 4th groups of noise exposure, where average freezing score was much less and conditioned by the anxiolytic effects of adrenoblockers, especially of mesedin. The restorative effect of mesedin was observed after 60 days of the noise action, where the average freezing score was much less in the 4th group, comparably to the 1st and the 2nd group rats.

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 [24]. The fact, that the hippocampus is affected by noise, is well documented [13, 13]. 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 [39].

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 a large number of incorrect alternations in the noise group. Correct alternations were considered to be BAC, CBA or ACB, etc., but in the noise group there was predominant BBA or AAC and other type of 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 -adrenoblockers decreased noise-induced stress and thus, restored anxiety-induced spatial memory. Interestingly, there was a difference in the effects of beditin and mesedin, since the beditin group number of alternations sequences was similar to the control, but the mesedin group rats manifested the highest number of alternations sequences, even compared to beditin.

The glutamate neurotransmitters system is crucial in cognition and its associated disorder. Integration of excitatory and inhibitory signals is a basic attribute of neuronal networks and the synaptic plasticity. When stress is moderate in the initial stages there is a development of adaptive mechanisms. The chronic stress gradually results in exhaustion and some unfavorable changes such as hyperactivity of the HPA-axis with overproduction of excitatory transmitters and attenuation of inhibitory GABAergic control [39].

The results of our study indicated onto the resistance phase of adaptation on the 30th day and rehabilitation dynamics after the noise-induced impairments. Adrenal cortical hormone and epinephrine elevation was consistent with the sympathetic nervous system activation [40], known as the "fight or flight" response of organism [41]. Anyway, the chronic noise action (till the 60-th day) lead to the exhaustion phase of stress with appearing of the cognitive dysfunction and upregulation of MDA levels.

Our results obtained apparently indicated, that rats of the 2nd group were more anxious compared with those in the 3rd and 4th group. With the OFT study our results had shown that under the chronic noise action entries of animals into the periphery zone and average freezing score were more expressed, rather than in the central zone, which is assumedly conditioned by their anxiety level induced by noise (that was well expressed in the noise group rats). The increased levels of anxiety were accompanied by the immobility and disturbance orientation of rats. The latter was expressed by the fact, that animals spent longer periods of time in the periphery zone of the open field or under the wall of one the Y-maze's arms. 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 open field and 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

locomotive, behavioral activity and increased anxiety levels causing a noise duration-dependent deficit in spatial memory in rats. 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 selective α_2 -adrenoreceptor blocker mesedin can be considered as a valuable drug candidate in the comprehensive limitation and treatment of stressful 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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Authors' contributions

Conceptualization, Ashkhen Manukyan and Magda Melkonyan;

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Writing—original draft preparation, Ashkhen Manukyan;

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Figures

Figure 1

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 considered to be 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.

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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 considered to be 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 2

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 2

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 3

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.

Figure 3

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.

Figure 4

Number of entries to the periphery zone (each group is of 6 animals, under the 8hr noise /day action). Thus after 7, 30 and 60 days of noise action the rats of the 2nd group have had146,4%, 140,8%, 123,2% number of entries to the periphery zone compared with the1stgroup (in which the activity was considered to be as 100%), respectively, the rats of the 3rd group spent 95%, 64,7%, 64,8%, respectively and the rats of the 4th group spent 70,4%, 80,9%, 47,1%, respectively.

Figure 4

Number of entries to the periphery zone (each group is of 6 animals, under the 8hr noise /day action). Thus after 7, 30 and 60 days of noise action the rats of the 2nd group have had146,4%, 140,8%, 123,2% number of entries to the periphery zone compared with the1stgroup (in which the activity was considered

to be as 100%), respectively, the rats of the 3rd group spent 95%, 64,7%, 64,8%, respectively and the rats of the 4th group spent 70,4%, 80,9%, 47,1%, respectively.

Figure 5

Average freezing score (each group is of 6 animals, under the 8hr noise /day action). Therefore, after 7, 30 and 60 days of noise action the rats of the 2nd group have had 185,4%, 122,9%, 158,5% average freezing score compared with the 1st group (in which the activity was considered to be as 100%), respectively, the rats of the 3rd group spent 124,8%, 90,1%, 69,9% respectively and the rats of the 4th group spent 121,7%, 84,4%, 54,3%, respectively.

Figure 5

Average freezing score (each group is of 6 animals, under the 8hr noise /day action). Therefore, after 7, 30 and 60 days of noise action the rats of the 2nd group have had 185,4%, 122,9%, 158,5% average freezing score compared with the 1st group (in which the activity was considered to be as 100%), respectively, the rats of the 3rd group spent 124,8%, 90,1%, 69,9% respectively and the rats of the 4th group spent 121,7%, 84,4%, 54,3%, respectively.