Adrenergic Alpha-2 Receptor Antagonists Cease Augmented Oxidation of Plasma Proteins and Anxiety of Rats Caused by Chronic Noise Exposure

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Abstract

Background: Noise is one of the environmental factors, which is considered as a powerful stressor for the organism. Generally, the acoustic stress affects the behavior and physiological state of humans and animals. Aims: The goal of this study is to investigate the relationship between chronic noise exposure and the effects of adrenergic alpha-2 receptor antagonists, beditin and mesedin, on the anxiety and oxidation of plasma proteins and fibrinogen in rats. Methods: The experiments were carried out on non-linear albino male rats, divided into four groups (six animals in each): 1. Healthy controls 2. Exposed to noise of a level 91 dB(A), eight hours daily, during 7, 30 and 60 days; 3. Injected with 2 mg/kg of beditin (2-(2-amino-4-thiazolyl)-1,4-benzodioxane hydrochloride)); 4. Injected with 10 mg/kg mesedin (2-(2-methyl-amino-thiozolyl)-1,4-benzodioxane hydrochloride). For evaluating the cognitive impairment, the Any-maze test was applied. The level of carbonylation of proteins was assessed by reaction with 2,4-dinitrophenylhydrazine, spectrophotometrically. Results: Chronic noise decreased locomotor activity and increased anxiety and oxidation of plasma protein and fibrinogen. Intensity of these changes were dependent on the duration of noise exposure. Conclusion: The Alpha 2 adrenoblockers alleviate oxidative modification of plasma proteins and reduce the cognitive impairment caused by chronic exposure to noise.

Keywords: Anxiety, beditin, mesedin, noise, oxidative stress, sympathetic nervous system

INTRODUCTION

Observational and experimental studies have showed that chronic noise exposure is related to annoyance and sleep disorders,[1] atherosclerosis, hypertension,[2,3] the impairment of cognition and hearing.[4,5] The development of these pathological states is associated with free-radical oxidative processes intensification, leading to the oxidative modification of proteins, peroxidation of membranes phospholipids and lipoproteins,[2,6] and finally resulting in functional disturbances in different tissues. Any stress is accompanied with impairment of cognition which can be estimated by behavioral tests.[7] It is largely accepted that hippocampus plays a pivotal role for regulation of mood and cognitive functions involving mainly alfa2 adrenoceptors,[8] blockage of which expresses high regulatory effect in stress conditions.[9] An implementation of antioxidants in stressful

Key massage

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situations, shown in multiple studies, reduces the stress-induced metabolic and functional deviations by means of regulation of oxidative stress intensity.\(^\text{[6,7]}\) The use of antioxidants does not always render sufficient protection while exposed to hazardous noise levels,\(^\text{[10]}\) although it may diminish the noise-induced symptoms. Therefore, there is a growing interest in a search for new approaches and ways to solve this problem. Studies of compounds with pronounced modulatory effects on the sympathoadrenal system, while exhibiting an antioxidant effect when exposed to occupational noise, are currently an urgent problem.\(^\text{[9]}\) In our previous studies the adrenergic alpha-2 receptor antagonists have been demonstrated to be efficient in noise conditions, as a particular case of stress-reaction mediated through the sympathetic nervous system.\(^\text{[11]}\)

Some antioxidant properties of adrenergic alpha-2 receptor antagonists mesedin and beditin in acute stress models were also revealed.\(^\text{[12]}\) Among the adrenergic alpha-2 receptor antagonists, mesedin (2-(2-methyl-amino-thiozolyl)-1,4-benzodioxane hydrochloride), and beditin (2-amino-4-thiazolyl)-1,4-benzodioxane hydrochloride), were chosen because of their stable blocking of the α2-adrenoreceptors, lower toxicity, and improved survival of animals compared to other Adrenergic alpha-2 receptor antagonists, such as idazoxan.\(^\text{[13-15]}\) Implementation of mesedin and beditin as antistressor compounds in acoustic stress recorded sufficient regulative effect on the intensity of lipid peroxidation as decrease in MDA.\(^\text{[12]}\) The open field test\(^\text{[16-18]}\) which is broadly used to estimate the behaviour in animals under the stressful conditions, revealed decrease in anxiety of rodents under the chronic noise action.

The aim of this study is to investigate how adrenergic alpha-2 receptor antagonists modify the effects of chronic noise on the oxidation of plasma proteins and fibrinogen and anxiety in rats.

**ANIMALS AND METHODS**

**Animals**

We used non-linear albino male rats weighing 150–200 g kept in ordinary vivarium conditions, maintained on a 12-h light/dark cycle with food and water at libitum in accordance with the European Communities Council Directive (86/609/EEC) on care and use of animals for experimental procedures; protocol was approved by the Institutional Animal Care and Ethics Committee. Specific *in vivo* conditions for each experiment were kept: temperature 20°C, humidity 52%. The animals were divided into 4 groups (six animals in each): 1. Healthy controls; 2. Exposed to noise of a level 91 dB(A), eight hours daily, during 7, 30 and 60 days; 3. Injected with 2 mg/kg of beditin (2-(2-amino-4-thiazolyl)-1,4-benzodioxane hydrochloride) intraperitoneally, 12hr prior to exposure to noise; 4. Injected with 10mg/kg mesedin (2-(2-methyl-amino-thiozolyl)-1,4-benzodioxane hydrochloride) 12hr prior to exposure to noise. Injections were repeated every 24 hr.

**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 10,000–16,000 Hz. The noise level was set at 91 dBA (60 consecutive days, 8h per day, from 1:00 to 9:00 a.m. automatically plug in)\(^\text{[19]}\) and was uniform inside the cage, as monitored with a sound meter (ST 11 D).

**Protein carbonyl content assay**

Blood was taken by cardiopuncture, in heparinized syringes, using Ketamine anesthesia (0.5–0.75 mg/kg IP). Proteins carbonyl content was measured to determine the level of oxidative modification of proteins. Carbonylation was measured by the method of Levine et al.\(^\text{[20]}\) using the reaction with 2,4-dinitrophenylhydrazine (DNPH), in the blood plasma. Spectrophotometer Hitachi 150-20 UV–vis (Japan) was used for the absorbance measurements.

**Fibrinogen carbonylation assay**

Fibrinogen was precipitated from 0.1 ml of citrated plasma by the addition of 12.7% (w/v) aqueous sodium sulfate (Na₂SO₄) solution, up to final concentration of 10.67%.\(^\text{[21]}\) The solution was, then, incubated at 37°C for 2 hours and then centrifuged at 2000 × g for 10 minutes. The pellet was washed three times with 5 ml of 10.67% Na₂SO₄ and mixed with 1 ml of 20 mM 2,4-DNPH.\(^\text{[22]}\) The amount of DPNPs formed and protein concentration were measured as described above.

**Open field**

A square open field\(^\text{[23]}\) is represented by a wooden square-shaped plate (60 × 60). From edges the plate was covered by walls of 20 cm height. The rats were placed in the middle of the plate, then the animal behavior was observed during 5 minutes. Each trial was recorded for later analysis, using a video camcorder positioned 2.1 m above the apparatus. The number of entries to deferent zones and the average freezing score were compared within the groups.

**Procedure**

Rats were carried to the test room from their home cages and were handled by the base of their tails at all times. Rats were placed into the center of the open field and allowed to explore the apparatus for 5 minutes. After the 5 minutes test, the rats taken back to their home cages and the open field was cleaned with 70% ethyl alcohol and permitted to dry between tests.

**Analyses**

The analysis was performed using Any-maze system. Any-maze is a video-tracking system, which analysis the subject tracks using subject location and movement. The track analysis is based on arena settings. The arena settings...
define a variety of zones or locations inside the arena, where the behavior parameters will be measured. Behavior is defined in terms of locomotion or position.

**Statistical analysis**

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**

We found a relationship between the duration of noise exposure and the concentration of the protein oxidation carbonyl products both in plasma proteins and fibrinogen [Figure 1]. The noise-induced protein oxidation intensity was reduced by mesedin and beditin. Intraperitoneal administration of mesedin and beditin decreased the content of modified fibrinogen [Figure 2] which depends on the duration of noise action.

Behavioral and locomotive activity in the open field was estimated by the time in the center zone, which is an indicator of the level of anxiety (negative relationship). Rats exposed to noise only spent less time in the center compared to rats injected with mesedin and beditin before exposure to noise [Figure 3].

The rats were injected mesedin and beditin prior to noise exposure spend a shorter time in the periphery

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**Figure 1:** Carbonylation of plasma proteins (each group is of 6 animals, under the 8 hr noise/day action). According to the data after 7, 30 and 60 days of noise exposure the 2nd group rats’ oxidative intensity level compared with the 1st group (which was accepted to be as 100%), was 127.2%, 110%, 119%, the rats of the 3rd group have had 87.1%, 92.8%, 85.3%, and the rats of the 4th group have had 85%, 89.9%, 85.3%, respectively

**Figure 2:** Carbonylation of plasma fibrinogen (each group is of 6 animals, under the 8 hr noise/day action). According to the data after 7-, 30- and 60 days of noise impact the 2nd group rats fibrinogen carbonylation level was 125.5%, 112.4%, 156% compared with the 1st group (was considered to be as 100%), the rats of the 3rd group have had 100.7%, 79.5%, 118.2%, and the rats of the 4th group have had 101.4%, 72.2%, 101.4%, respectively
zone which could be due to their anxiolytic effect [Figure 4].

Figure 5 shows data of the total freezing episodes in the open field test. Freezing behavior is the total amount of time that the rat spends lying or sitting with the body motionless. Rats exposed to noise spent more time motionless compared to controls. The rats’ motor activity was increased under noise if they were injected with mesedin and beditin beforehand [Figure 5].

**DISCUSSION**

The data obtained indicated an increase in anxiety and the level of oxidatively modified plasma proteins and fibrinogen of male rats exposed to chronic noise. Alpha 2 receptor antagonists, mesedin and beditin, significantly decreased noise-induced deterioration in anxiety and the plasma proteins carbonylation.

It is known that any stressful effect causes both the activation of the sympathoadrenal system and the development of oxidative stress, two non-specific processes responsible for the functional stability of the body. Observed excess generation of carbonyl derivatives of plasma proteins and fibrinogen under the chronic loud noise takes place to an activation of the peroxidation processes with increased reactive oxygen species (ROS) formation. In this respect malondialdehyde (MDA) as an indicator of lipid peroxidation has an important role in oxidative stress evaluation. The attack of proteins by ROS can lead to amino acid sidechain modifications, cleavage of protein backbone, and formation of crosslinked protein complexes.

Our previous study showed that acute noise action increased level of oxidatively modified proteins in the plasma and the erythrocytes membranes of the experimental animals. In the given study we have shown that chronic noise impact increased carbonylation of plasma proteins.
proteins of the noise-exposed rats, so the modified plasma proteins also can serve as markers of oxidative stress.

It is shown that α2 antagonists improve memory and cognition, spatial cognitive performance in a number of tests.[8] Yohimbine and idazoxan, widely used α2 antagonists, enhance passive avoidance learning.[27] Yohimbine effectively improves accuracy and response latencies in the habituated animal.[28] Dextefaroxan improves odor learning.[29] Spatial and visual memory, passive avoidance.[30] Moreover, α2 antagonist atipamezole enhances spatial learning in aged rats.[31] In all the used models of stress in mentioned studies were described developed level of oxidation and high efficiency of antioxidant impact.[32,33] Trying to explore the mechanisms of possible protective effects of alpha-2 receptor antagonists on the development of oxidative stress and behavioral deviations under chronic exposure to noise, and taking into account abovementioned, we implemented mesedin and beditin to noise-treated rats and recorded less oxidation intensity levels of the plasma proteins in the studied groups.

The analysis of oxidative modifications in plasma proteins is the most informative approach in investigation of the oxidative stress role in the certain pathology development. Interestingly, oxidative stress may lead to the certain modifications of FG,[34] resulting in alterations of its biological properties.

Our results have shown that chronic noise increased carbonylation intensity of FG, high-molecular plasma protein and the basic plasma coagulation factor, in the noise-exposed rats.[35] Oxidatively modified FG was found to modulate blood rheological parameters.[36] Our results are evidence of decreased content of modified FG in plasma after 30 and 60 days of the noise action in mesedin and beditin treated animals.

Fibrinogen plasma content could have a clinical diagnostic significance, as at the adaptation stage of the noise-induced stress and by the mesedin administration its level becomes even less than in the control group.

According to the results got, the time spent in the different zones changes dependently on increase of anxiety under the noise-induced stress action. A long time spent in the central zone was also an evidence of absence or low level of anxiety. Our results have shown increased anxiety level of the rats exposed to noise, which was expressed by less time in the center. The restorative effects of beditin and mesedin were observed after 60 days of the noise action, which was expressed by the rats of the third and fourth groups spent more time in the center.

Harmful effects of noise were observed during the survey of the time in the periphery zone. The noise group rats had higher score of this parameter, rather than in the control, beditin and mesedin groups because of high anxiety level, which resulted in low locomotor behavior.

By estimation of behavioral activity and level of anxiety an important parameter was the total freezing episodes in the open field test under the acoustic stress conditions. Freezing behavior is the total time that the rat spends lying or sitting with the body motionless, except for slow lateral movements of the head or the ones needed for breathing. Chronic noise decreased locomotor activity of the noise group rats, which was in accordance with the total freezing episodes score. The motor activity increased by influence of alpha-2 receptor antagonists, which was expressed by that the rats of the third and fourth groups had higher number of freezing episodes. In mesedin-treated rats there was recorded a higher score total freezing episodes (detected by means of the roaring and grooming intensity in the freezing episodes),

Figure 5: Total freezing episodes (each group is of 6 animals, under the 8 hr noise/day action) in the open field. Therefore after 7, 30 and 60 days of noise action the rats of the 2nd group have had 51.5%, 96.6%, 80% total freezing episodes compared with the 1st group (in which the activity was considered to be as 100%), the rats of the 3rd group spent 59.7%, 110%, 94.6%, and the rats of the 4th group spent 57.8%, 111.5%, 111.5%, respectively.
so the mesedin effect was more expressed compare with beditin. This anxiogenic effect may originate from the HIP circuit or be provoked by extra-hippocampal inputs. Taking into account the aforementioned results, we can highlight different changes in cognition.[37] These changes are HIP-associated and influence on integration of cognitive information and the responses management to noise-induced alterations.

According to our data, on the 30th day of noise exposure the “General Adaptation Syndrome” to the harmful effect of noise was noticeable. This syndrome is mediated by intense and persistent stressors that produce a specific effect on the adrenal glands.[38] Our data showed that the animals were in a resistance phase of adaptation on the 30th day and had a tendency to recover from the effects of noise exposure. At this stage, it was observed, that high levels of adrenal cortical hormone and epinephrine alongside the increased activity of the sympathetic nervous system. All these changes were preparing the animals for the “fight or flight” response.[39] However, persistent noise exposure (until day 60) eventually resulted in an exhaustion phase where the harmful effects, namely cognitive dysfunction, became evident.

Based on our results, the noise-exposed rats were more anxious than those of administered mesedin and beditin. The increased levels of anxiety were expressed by shorter periods of time spent in the central zone of the open field. Thus, noise-induced stress can mimic anxiety-related behavior changes by triggering a release of norepinephrine in the central and peripheral nervous systems. This pattern was changed by injection of the alpha-2 receptor antagonists. Our results showed that chronic administration of alpha-2 receptor antagonists led to the inhibition of α2-adrenergic activity, the reduction of stress-related anxiety levels. According to the results of behavioral observations in the open field test, the alpha-2 receptor antagonists significantly reduced the stress-induced immobility of rats after 60 days of the persistent noise exposure. The anxiolytic action of alpha-2 receptor antagonists in the rats of mesedin and beditin groups was demonstrated via decreased anxiety levels and increased overall locomotor function.

CONCLUSION

Alpha-2 receptor antagonists, mesedin and beditin, significantly ceased anxiety of rats caused by chronic noise exposure. Findings of this study demonstrated that plasma oxidative modified proteins/fibrinogen can be used as a biomarker in the case of chronic noise exposure.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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