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Effects of Chronic Noise Exposure on Spatial Learning and Memory of Rats in Relation to Neurotransmitters and NMDAR2B Alteration in the Hippocampus

Bo CUI, Mingquan WU and Xiaojun SHE

Department of Occupational Hygiene, Institute of Health and Environmental Medicine, PR China

Abstract: Effects of Chronic Noise Exposure on Spatial Learning and Memory of Rats in Relation to Neurotransmitters and NMDAR2B Alteration in the Hippocampus: Bo CUI, *et al*. Department of Occupational Hygiene, Institute of Health and Environmental Medicine, PR China—Objectives: The purpose of this study was to examine the effects of noise exposure on spatial learning and memory and associated mechanisms in the hippocampus (HIP). **Methods:** Forty-eight male SD rats were grouped as: A, control; B, Morris water maze (MWM) training group; C, noise exposure group; and D, noise exposure followed by MWM training group. The influence of noise stress on spatial learning and memory in rats was assessed in hidden platform acquisition training and probe trial testing in MWM. Changes in morphology of Nissl bodies were observed in the CA1, CA3 and DG regions of HIP. In order to understand the possible mechanisms behind noise stress-induced changes, the concentration of amino acid neurotransmitters and the expression of NMDAR2B (NR2B) in HIP were also evaluated. **Results:** After noise exposure, the performance of spatial learning and memory in group D was decreased significantly compared to group B. The concentration of glutamate was significantly increased in groups C and D, whereas GABA decreased markedly. The mean optical density of Nissl bodies in groups C and D was reduced in the CA1, DG and CA3 regions. The expression of NR2B was significantly decreased in the CA1, CA3 and DG regions in group C, and in the CA1 and CA3 regions in group D as compared with groups A and B. **Conclusions:** Excitotoxicity, impaired Nissl bodies and reduced expression of NR2B in rat HIP induced by chronic noise exposure might have caused the impairment of spatial learning and memory.
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Key words: Learning and memory, Neurotransmitters, Nissl bodies, Noise, NR2B

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Correspondence to: M. Wu, Department of Occupational Hygiene, Institute of Health and Environmental Medicine of Tianjin, 1 Dali Road, Heping District, Tianjin 300050, PR China (e-mail: tjwmq@126.com)

Noise has always been an important environmental problem for mankind. With rapid industrialization in modern society, noise pollution is on an ever-increasing trend, both in industrial areas and general areas. The WHO document on the Guidelines for Community Noise indicated that noise exposure may lead to many detrimental effects including hearing impairment; psychophysiological, mental-health and performance effects; effects on residential behaviour and annoyance[1]. It has been documented in both laboratory subjects and in workers exposed to occupational noise that noise adversely affects cognitive task performance. In children, too, environmental noise impairs a number of cognitive and motivational parameters[2–7]. In the short term, noise-induced arousal may produce better performance of simple tasks, but cognitive performance deteriorates substantially for more complex tasks (i.e. tasks that require sustained attention to details or to multiple cues; or tasks that demand a large capacity of working memory). Among the cognitive effects, reading, attention, problem solving and memory are most strongly affected by noise. Spatial learning and memory are coordinated by different brain regions, especially HIP. A study carried out on animals showed that chronic noise-induced oxidative stress, increased acetylcholinesterase activity, reduced dendritic count in HIP mPFC regions, elevated the plasma corticosterone level, and might have caused the impairment of spatial memory[8]. However, the advanced mechanisms responsible for chronic noise-induced cognitive impairment are not well understood.

Amino acid neurotransmitters and NMDA receptors play important roles in cognition. It is known that both

acute and chronic noise exposure can alter the brain biogenic amine levels, e.g. those of norepinephrine, epinephrine, dopamine, and serotonin[9, 10]. However, little is known about the changes of amino acid neurotransmitters and NMDA receptors in HIP in the pathogenesis of cognitive impairment induced by noise exposure.

The aim of this study was to further investigate the effects of chronic noise exposure on spatial cognition. To understand the mechanism of noise exposure on cognitive alteration, we studied the morphology of Nissl bodies and the level of amino acid neurotransmitters as well as the expression of NR2B in HIP.

Materials and Methods

Animal use and experimental grouping

Healthy adult male Sprague Dawley rats weighing 200–220 g (6–7 wk of age) were used in this study. The rats were kept in a room with controlled ambient temperature (25 ± 2°C), humidity (50–70%) and a 12-h light/dark cycle (light on from 06:00–18:00 h). They had free access to water and food in their home cages and were allowed to adapt to our laboratory environment for 5 days before the start of the experiment. The animal use protocol was approved by the Animal and Human Use in Research Committee of The Institute of Health and Environmental Medicine, Tianjin, PR China.

The animals were randomly divided into four groups:

Group A: controls with neither noise exposure nor MWM training, n=12;

Group B: MWM training (hidden platform testing: from experimental day 26 to 29; probe trial: on the experimental day 30; start at 14:00 every training day), n=12;

Group C: noise exposure (100 dB white noise, 4 h / day × 30 day, from 8:00 to 12:00) without MWM training, n=12;

Group D: noise exposure as Group C, followed by MWM training as in Group B, n=12.

Setups for noise exposure

The white noise was generated by using a noise generator (Bruel and Kjaer Instruments, 1027), amplified with a power amplifier, and delivered to a loudspeaker. All exposures were carried out in a reverberation chamber, and the animals were housed in wire-mesh cages placed in the center of the sound field, with one animal per cage. The loudspeaker was suspended directly above the cage. Noise levels were measured with a sound level meter (Bruel and Kjaer Instruments, 2209), using linear weighting at the level of the animals' ears. The noise level variation was less than 2dB within the space available to the animal. The background noise level in the chamber was below 40 dB SPL (sound pressure level).

Morris water maze testing

A circular pool (diameter, 100 cm; height, 50 cm; depth of water, 32 cm) was used in these experiments. The platform (diameter, 10 cm) was 2 cm below the water surface during training. The water was kept at 23 ± 2°C and made opaque with white comminuted foamed plastics. The pool was situated in a room with visual cues. The animals' movements were recorded with a video camera attached to the ceiling. The pool was divided into four arbitrary quadrants for transfer test analysis. The quadrant in which the platform was located was designated the target quadrant. During task aquisition, the program measured the latency of animals to reach the platform and the time animals spent in the target quadrant. Animals were placed in the water at one of four starting positions that alternated in a clockwise manner. Four trials were performed per day, and the intertrial interval was about 5 min. The cut-off time for a trial, if the animals failed to locate the platform, was 60 s; in such cases the animals were manually placed on the platform for 10 s. On day 5, the platform was removed, and each mouse was placed in the pool once for 60 s, starting from the same starting location as was used first in the hidden platform testing. The time spent swimming in the quadrant where the platform had been was recorded. This is considered to be the most specific test for spatial memory[11].

Amino acid neurotransmitter assays

The rats were sacrificed by decapitation immediately after the last noise exposure and MWM training. The HIP region in right hemicerebrum was collected, and the concentration of amino acid neurotransmitters, including glutamic acid (Glu), gamma-aminobutyric acid (GABA), aspartic acid (Asp) and glycine (Gly), were measured using an HPLC-EC system (600E Liquid chromatography, Waters). The HPLC system was equipped with a reverse-phase column (C18, 150 mm × 4.6 mm, 5 μm; Tridimensional Chromatography, Tianjin, China), coupled with electrochemical detection. The samples were homogenized in 0.1 M perchloric acid containing dihydroxy-benzylamine (DHBA), and centrifuged at 14,000 rpm for 20 min at 4°C. The supernatant affiliated with $NaHCO_3$ and dinitrofluorobenzene (DNFB) was placed in bain-marie at 70°C for 20 min, and then injected into the HPLC-EC system. The mobile phase contained sodium acetate buffer (pH=6.4) and 50% acetonitrile with a ratio of 72:28. The column temperature was set at 35°C, and the detection wavelength was 360 nm.

Tissue preparation for Nissl staining and immunohistochemistry

For histology, the animals were anesthetized with pentobarbital sodium and perfused transcardially with 0.1

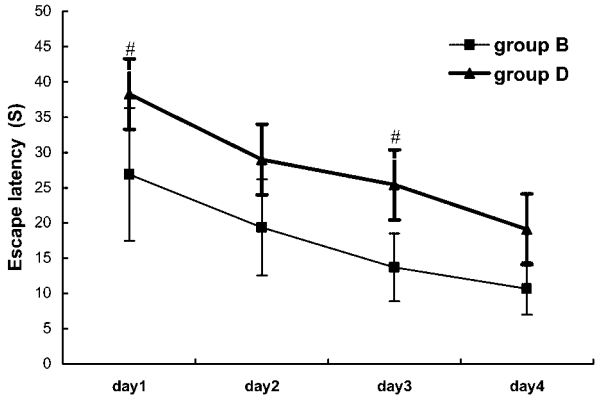

Fig. 1A. The effect of noise exposure on escape latency in hidden-platform acquisition testing. Escape latency, in seconds, to reach the platform during each trial. #p<0.05 vs. group B.

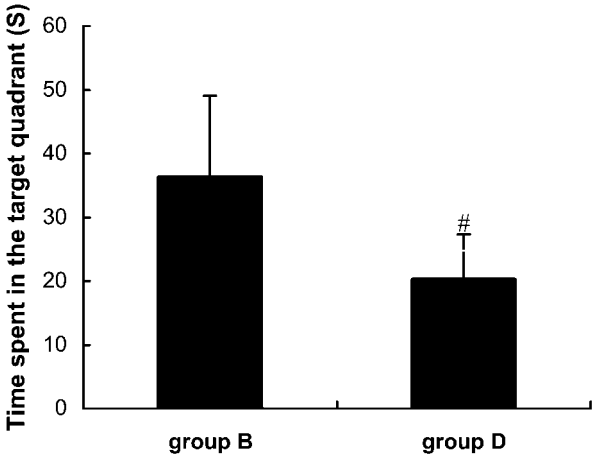

Fig. 1B. The effect of noise exposure on time spent in target quadrant in probe trial testing. #p<0.05 vs. group B.

M phosphate-buffered saline (PBS, pH 7.4) followed by 4% paraformaldehyde in 0.1 M PB (pH 7.4) at the designated times after the surgery. Brains were removed and post-fixed in the same fixative for 48 h, then dehydrated in alcohol (70%, 80%, 95%, 100%). The process for the paraffin embedding schedule was as follows: xylene, three changes, 1 h each; paraffin wax (56–58°C), two changes, 1 h and half each; embedding of tissues into paraffin blocks. Then,the paraffin blocks were trimmed as necessary and cut at 8 μm with paraffin section cutter. The coronal sections were then mounted onto polylysine-coated glass slides. Before Nissl staining and immunohistochemistry, paraffin sections were deparaffinized in xylene (2 or 3 changes) and hydrated in alcohol (100%, 95%, 70%) to tap water, then rinsed in distilled water.

Nissl staining with toluidine blue

Tissue slices were immersed in 0.1% toluidine blue (Sinopharm, China) for 10 min and rinsed with distilled water. Then, brain slices were progressively dehydrated in 70% alcohol (for 5 min), 95% alcohol (with a few drops of 10% acetic acid) (for 2 to 3 min) and finally 100% alcohol (for 5 min). Slices were subsequently cleaned in xylene for 3 min before being covered with resin and a coverslip.

Immunohistochemistry for NR2B

The deparaffinized sections were labeled in a moist chamber by immersing them in drops of solution in the following sequence (the number of repeated steps is given in square brackets): 0.3% H_2O_2 for 5 min; 0.05 M Tris-buffered saline, pH 7.4 (TBS) containing 0.1% Triton X-100 for 5 min [× 3]; 10% horse blocking serum in TBS for 10 min; mouse monoclonal antibody to NR2B (Boster, China) at 1/100 dilution in TBS containing 1% bovine serum albumin (BSA) for 2 h at 37°C, then overnight at 4°C; TBS for 5 min [× 3]; anti-mouse Bio-IgG diluted 1/150 in TBS for 45 min at 37°C; TBS for 5 min [× 3]; HRP-SA diluted 1/200 in TBS for 45 min at 37°C; TBS for 5 min [× 3]; DAB staining for 10 min; distilled water rinsing; hematoxylin staining for 30 s; distilled water rinsing; and finally they were covered with resin before microscopic observations.

Image data analysis

Nissl stained and immunohistochemical sections were analyzed quantitively for 3 slices per rat and 3 rats per group were used. The region of interest (ROI) was taken from matched littermate pairs of sections and the mean optical density (MOD) for each ROI was determined using a CMIAS image analysis system (Bei Hang University, Beijing, China).

Statistics

Data are expressed as mean ± SD. Unless specified otherwise, data were analyzed by one or two factor ANOVA (general linear model) tests using the statistical software SPSS 13.0 (SPSS Inc.). A value of p<0.05 was considered to be statistically significant.

Results

The effects of noise exposure on spatial learning and memory

As shown in Figs. 1A and 1B, during the stage of hidden platform acquisition training, rats of both groups B and D improved their performance as indicated by the decreasing escape latencies across successive days. The escape latency was in a general higher trend in group D than in group B, and statistically significant changes were

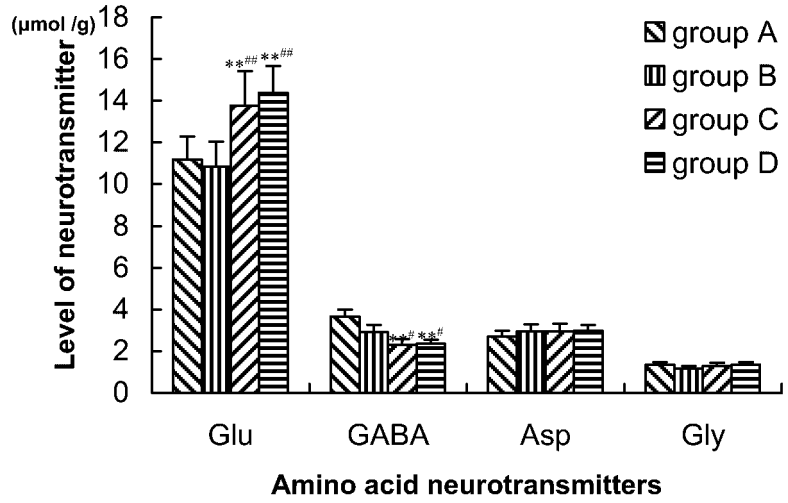

Fig. 2. The effect of noise exposure on level of amino acid neurotransmitters. $^{**}p<0.01$ vs. group A; $^{\#}p<0.05$, $^{\#\#}p<0.01$ vs. group B.

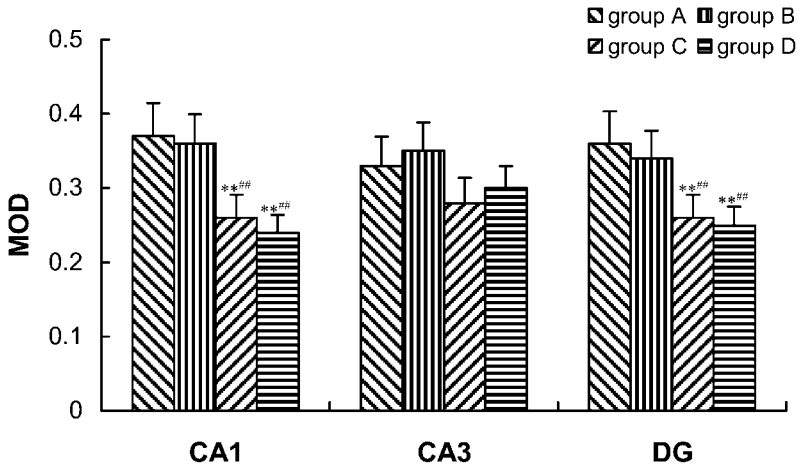

Fig. 3. The effect of noise exposure on Nissl bodies in different regions of the hippocampus. $^{**}p<0.01$ vs. group A; $^{\#\#}p<0.01$ vs. group B.

found at days 1 and 3 (day 1:38.3 s vs. 26.9 s, $p<0.05$; day 3: 25.4 s vs. 13.7 s, $p<0.05$). During the stage of probe trial testing, the time spent in the target quadrant was significantly decreased in group D compared with group B (20.2 s vs. 36.3 s, $p<0.05$).

Changes of amino acid neurotransmitters

As shown in Fig. 2, chronic noise exposure caused a significant increase in the level of Glu ($F=48.078$, $p<0.01$) and a significant decrease of GABA ($F=24.996$, $p<0.01$), although the levels of Asp and Gly were not significantly changed after noise exposure. However, two-way ANOVA revealed no significant effect of MWM training on levels of amino acid neurotransmitters.

Changes of Nissl bodies

As shown in Fig. 3, the values of MOD were reduced significantly in the CA1 and DG regions in group C and D rats that were exposed to noise, whereas they were not significantly different in the CA3 region after noise exposure. In contrast to the noise exposure, there was no significant effect of MWM training on Nissl bodies.

Changes in NR2B immunoreactivity

As shown in Fig. 4, the expression of NR2B decreased in the CA1, CA3 and DG regions after noise exposure, with group C showing the lowest levels. However, two-way ANOVA showed no significant effect of MWM training on expression of NR2B in the CA3 region.

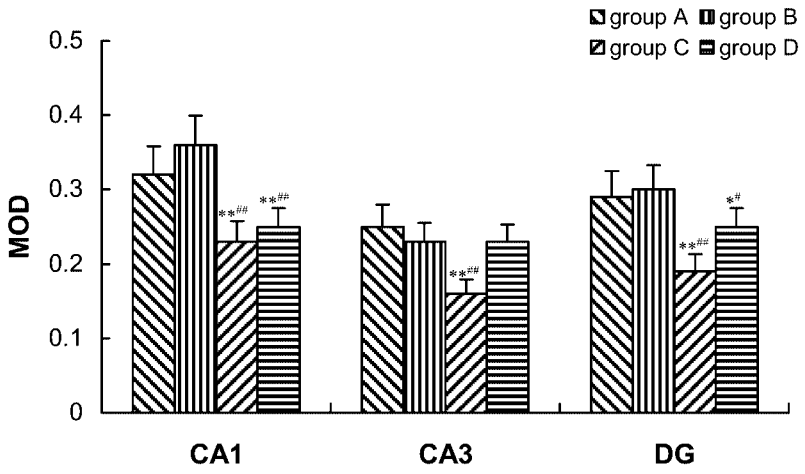

Fig. 4. The effect of noise exposure on expression of NR2B in different regions of the hippocampus. *p<0.05,**p<0.01 vs. group A; $^{\#}p$<0.05, $^{\#\#}p$<0.01 vs. group B.

Discussion

The present study showed the effects of chronic noise exposure on spatial learning and memory, amino acid neurotransmitters and Nissl bodies and NR2B in the CA1, CA3 and DG regions of HIP of male rats. Forced swimming in MWM is a stressor that may have effects on HIP, so it was considered as a grouping factor as well as noise exposure in this study, and our results show limited effects of MWM training on HIP.

Noise is an environmental stress. Chronic noise stress impairs cognition in a number of aspects, such as acquisition of memory, consolidation and recall[11, 12]. There are clear indications that chronic stress results in persistent memory impairments, psychiatric disorders, post-traumatic stress disorder and dissociative disorders[13]. Noise intensity for the study of effects of noise on the functions of central neural system has typically ranged from 100–120 dB[8–10]. In this study, we chose noise of 100 dB for 4 h per day for 30 days as chronic noise, according to previous studies and our experimental experience.

The MWM is generally considered to be a test of spatial learning and memory. MWM performance involves several components, including concept formation (learning the general rules of the task), attention, working memory, and reference memory. The hiddenplatform test and probe trial test are considered to be the most specific tests for spatial learning and memory, respectively[14]. In our MWM test, when compared to the control, the animals exposed to noise stress showed significant increases in the escape latency (Fig. 1A) and significant decreases in the time spent in target quadrant (Fig. 1B). Our results correlate well with those of Manikandan[8], who revealed that noise exposure may cause impairment in spatial memory. Spatial learning and memory are associated with HIP, which is involved in the integration of cognitive and emotional information and in modulating hypothalamic-pituitary adrenal (HPA) responses to psychological stress. Learning and memory show an age-related decline and age-associated impairment extends to spatial memory tasks due to functional and morphological changes of the hippocampal formation[15]. In many pathological processes, such as post-traumatic stress disorder (PTSD) and age-associated impairment, HIP is the first brain region to show injury. Therefore, it is logical to postulate that changes in HIP, especially the amino acid neurotransmitters and their receptors, would be the most essential mechanisms of noise-induced cognitive impairment. However, this has not been addressed in the literature.

Alterations of the contents of amino acid neurotransmitters in the brain are associated with degenerative diseases of central nervous system (CNS), brain injury and cognitive impairment[16]. Studies in the past have dealt with the effects of aging on the excitatory amino acid neurotransmitter system which may contribute to age-related impairment of neurological function. Glutamate and GABA are the major excitatory and inhibitory neurotransmitters, respectively, in the CNS. Integration of excitatory and inhibitory signals is a basic attribute of neuronal communication. Thus, plasticity of synapses related to learning and memory requires adequate levels of excitation and inhibition to be maintained. When stress is moderate in the initial stages there is a development of adaptive mechanisms.

However, chronic stress gradually leads to exhaustion and to some disadvantageous changes such as excessive activity of the HPA-axis, overproduction by excitatory transmitters, and attenuation of inhibitory GABAergic control[17]. In this study, the increased content of Glu and decreased GABA in HIP of rats exposed to noise may have influenced the plasticity of synapses and, in turn, resulted in impairment in spatial learning and memory.

Nissl bodies are extranuclear RNA granules and are sites of protein synthesis; they may dissolve and disappear in pathological conditions. Our study showed that animals exposed to noise developed impairments of Nissl bodies in HIP, which means neuron function was decreased by noise. This might have been due to noise-induced pathology, such as excitotoxicity in HIP.

The glutamate neurotransmitter system has been implicated in cognition and its associated disorders. The NMDA receptor is a heteromeric ligand-gated ion channel that mediates synaptic functions such as long-term potentiation (LTP) and long-term depression (LTD)[18–21]. The NR2B subunit is a critical structural and functional component of the NMDA receptor and plays a major role in learning and memory[22–29], and, as a result, has been named the "smart receptor"[30]. In this study, we found that the expression of NR2B was significantly deceased in the CA1, CA3 and DG regions of HIP, but the mechanism behind this was not clear. It may be because of the loss of neurons in HIP, or as a result of internalization of NR2B. Receptor internalization is an universal phenomenon, a conjunction of ligands and their receptors[31]. In our study, the internalization of NR2B may have been caused by elevated Glu-induced over-activation of NR2B, resulting in its density in cell membranes being reduced, which might have modulated neuronal function as a feed-back. Besides, NMDA receptor is involved in plasticity, atrophy and in neuronal death in HIP[32]. Changes of the glutamate neurotransmitter system, including Glu and its NMDA receptor and GABA, might have played a role in the impairment of Nissl bodies, as well as atrophy of neurons in HIP[8], which in turn led to learning and memory impairment.

The results of the MWM tests presented in this paper confirmated the deleterious effects of chronic noise exposure on spatial cognition. Glutamate excitotoxicity, and disturbances in many neurotransmitter systems, especially disruption of the balance between the GABAergic inhibitory and glutamatergic excitatory systems, are probably the mechanisms underlying such neurocognitive deficits. However, to clarify the causal relationships between them, further studies need be performed. First, drugs which can inhibit spontaneous glutamate release should be used to examine whether the excitotoxicity of neurons, including impairment of Nissl bodies and NR2B, and the learning and memory deficits produced by noise exposure can be prevented. As well as Glu binding, NR2B may be internalized in a process that appears to mediate downregulation of NR2B, and it would be possible to observe the internalization process in isolated HIP neurons with laser scanning confocal microscopy to demonstrate this hypothesis. Besides, we have also considered that there may be other possible mechanisms, such as high Glu-induced overload of intracellular Ca^{2+} and apoptosis of neurons in HIP. All of possible mechanisms will be explored and verified in our in-depth study.

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