Original Article

Effect of Chronic Noise Exposure on Expression of N-Methyl-D-Aspartic Acid Receptor 2B and Tau Phosphorylation in Hippocampus of Rats*

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Abstract

Objective To study the effect of chronic noise exposure on expression of N-methyl-D-aspartic acid receptor 2B (NR2B) and tau phosphorylation in hippocampus of rats.

Methods Twenty-four male SD rats were divided in control group and chronic noise exposure group. NR2B expression and tau phosphorylation in hippocampus of rats were detected after chronic noise exposure (100 dB SPL white noise, 4 h/d×30d) and their mechanisms underlying neuronal apoptosis in hippocampus of rats with TUNEL staining.

Results The NR2B expression decreased significantly after chronic noise exposure which resulted in tau hyperphosphorylation and neural apoptosis in hippocampus of rats. Immunohistochemistry showed that the tau hyperphosphorylation was most prominent in dentate gyrus (DG) and CA1 region of rat hippocampus.

Conclusion The abnormality of neurotransmitter system, especially Glu and NR2B containing NMDA receptor, and tau hyperphosphorylation in hippocampus of rats, may play a role in chronic noise-induced neural apoptosis and cognition impairment.

Key words: Noise; N-methyl-D-aspartic acid receptor 2B subunit; Tau hyperphosphorylation; Apoptosis

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INTRODUCTION

With the rapid industrialization in modern society, noise pollution has become a severe social and public health problem. The World Health Organization (WHO) document, Guidelines for Community Noise, indicates that noise exposure may lead to many detrimental effects, including auditory and non-auditory effects[1]. Previous studies demonstrated that chronic noise exposure can obviously impair cognitive function[2-6]. Spatial learning and memory are coordinated with different brain regions, especially hippocampus. We have recently demonstrated that excitotoxicity, impaird Nissl bodies, and reduced NR2B expression in rat hippocampus induced by chronic noise exposure result in impairment of spatial learning and memory[7]. However, further studies are needed to clarify their causal relationship.

NMDAR, containing a major class of Glu receptors in mammalian brain[8-9], is a heteromeric ligand-gated ion channel that mediates synaptic functions such as long-term potentiation (LTP) and long-term depression (LTD)[10-11], and mediates opposing effect according to its localization.

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Stimulation of synaptic NMDAR induces prosurvival events, whereas activation of extrasynaptic NMDAR leads to excitotoxic death[12]. It was reported that although NR2A receptors are predominantly confined to synapses, NR2B containing receptors is particularly distributed in extrasynaptase[13]. It has been shown that extrasynaptic NMDAR plays an important role in tau toxicity[14]. Tau is central to the dynamics of microtubule assembly and hence neuronal physiology. Tau hyperphosphorylation makes it a toxic molecule by which it is unable to participate in normal microtubule dynamics and leads to disruption and inhibition of microtubule assembly[15]. Tau toxicity is accompanied by sustained and delayed activation of ERK, which is NMDAR-dependent and critically involved in cell death[16]. Moreover, stressful stimuli such as starvation and cold water stress can cause tau hyperphosphorylation in brain[17-18]. Therefore, whether noise exposure, an acoustic stressor, causes *in vivo* tau phosphorylation was observed in this study.

NR2B expression and tau phosphorylation levels were measured in hippocampus of rats after exposed to chronic noise. We have previously shown that chronic noise exposure increases glutamate contents in hippocampus[7] and glutamate excitotoxicity is correlated with neuronal apoptosis[19]. Thus, neuronal apoptosis in hippocampus was detected with TUNEL staining in this study.

MATERIALS AND METHODS

Animal Use and Grouping

Twenty-four male SD rats (Lab Animal Centre, Academy of Military Medical Sciences, Beijing, China) weighing 200-220 g (6-7 weeks of age) were used in this study. The rats were housed in a room with controlled ambient temperature (23±2 °C), humidity (50%-70%) with a 12-h light/dark cycle (from 06:00 to 18:00 h) with a free access to water and food. The animals were allowed to adapt to our laboratory environment for 5 days before experiment. The protocol of animal use was approved by the Research Committee of the Institute of Health and Environmental Medicine, Tianjin, China. The rats were randomly divided into chronic noise exposure group and control group, 12 in each group. Rats in chronic noise exposure group were exposed to 100 dB SPL (root mean square, RMS) white noise (4 h /d×30d, from 8:00 to 12:00) and those in control group were not exposed to chronic noise.

Noise Exposure Setups

White noise was generated using a noise generator (B&K Instruments, 1027), amplified with a power amplifier (YONG-SHENG AUDIO P-150D, Third Institute of China Electronic Technology Group, China), and delivered to a loudspeaker (ZM-16S, Tianjin Zenmay Electroacoustic Equipment Co., LTD., China). All exposures were carried out in a reverberation chamber, and the animals housed in wire-mesh cages were placed in the center of the sound field, 1 in each cage. The loudspeaker was suspended directly above the cages. Noise levels were measured with a B & K 3560 C-size front end and 4938 1/4″ pressure-field microphone (B&K Instruments, Denmark) at ear level of the animals. The main spectrum of noise emitted from the speaker ranged 400-6300 Hz (1/3 octave). The noise level variation was less than 2 dB within the space available to the animal. The background noise level in the chamber was below 40 dB SPL.

Immunoblot Analysis of NR2B and P-Tau (Thr205)

After the last noise exposure on Day 30, 6 rats were sacrificed immediately for NR2B and p-tau analysis, the hippocampus was dissected immediately for immunoblot analysis, and homogenized in ice-cold 50 mmol/L Tris–HCl (pH 7.4) buffer containing 1% Triton X-100, 0.2 mmol/L PMSF and 1 mmol/L EDTA. Homogenates were centrifuged at 12 000×g for 10 min at 4 °C. The supernatants were immediately placed in boiling water for 10 min. Samples (20 μg protein/lane) were run on 10% SDS–PAGE and transferred to nitrocellulose membrane after electrophoresis. Membranes were probed with rabbit polyclonal antibody to NR2B (1:500, Boster, China) or p-tau (Thr205) (1:1000, Bioworld Technology, USA), to recognize the tau phosphorylation in Thr205 or in mouse anti-GAPDH monoclonal antibody (1:1000, Santa Cruze, USA), which was used as a loading control, followed by 1:1000 peroxidase-labeled anti-rabbit or anti-mouse second antibody. After visualization with the ECL system, the integrated intensity value of immunoreactive signals was analyzed using the Gel-Pro 3.1 software (Media Cybernetics, USA).

Tissue Preparation for Immunohistochemistry and TUNEL Staining

The animals were anesthetized with

pentobarbital sodium and perfused with 0.1 mol/L phosphate-buffered saline (PBS, pH 7.4), followed by 4% paraformaldehyde in 0.1 mol/L PB (pH 7.4) at the designated time points after surgery. Brains were removed, post-fixed in the same fixative for 48 h and dehydrated in alcohol (70%, 80%, 95%, and 100%). The tissues were treated with xylene for 1 h with 3 changes, and then immersed in paraffin wax for one and a half hours at 56-58 °C with two changes. The paraffin blocks were cut into 8 μm-thich sections. The coronal sections were mounted onto polylysine-coated glass slides. Before immunohistochemistry, paraffin sections were deparaffinized in xylene (2 or 3 changes), dehydrated in alcohol (100%, 95%, and 70%) with tap water and rinsed in distilled water.

Immunohistochemistry for P-Tau (Thr205)

The deparaffinized sections were immersed in a moist chamber and treated with 0.3% H_2O_2 for 5 min, 0.05 mol/L TBS (pH 7.4) containing 0.1% Triton X-100 for 5 min [×3], blocked with 10% horse serum in TBS for 10 min, incubated with rabbit polyclonal antibody to p-Tau (Thr205) (Bioworld technology, USA) diluted at 1/100 in TBS containing 1% bovine serum albumin (BSA) for 2 h at 37 °C and overnight at 4 °C, TBS for 5 min [×3], anti- rabbit Bio-IgG diluted at 1/150 in TBS for 45 min at 37 °C, TBS for 5 min [×3], HRP-SA diluted at 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 covered with resin before observed under microscope (Olympus BX51, Japan). Immunohistochemistry-stained sections were analyzed quantitatively on 3 slices from per rat. Region of interest (ROI) was taken from the matched littermate pair of sections, and mean optical density (MOD) for each ROI was determined with the image analysis system (Image-Pro Plus 5.0, Media Cybernetics, USA).

TUNEL Staining

The deparaffinized sections were stained with the TUNEL using an *in situ* cell death detection kit (Roche Diagnostics, Bromma, Sweden)[19]. The incorporated nucleotides were detected with anti-digoxin-biotin antibody conjugated to horseradish peroxidase (Boster, Wuhan, China). TdT or anti-digoxin-biotin antibody was omitted in control incubation. After substrate reaction, stained cells in the sections were observed under light microscope. All sections were coded and evaluated independently by two investigators.

Statistical Ananlysis

All data were analyzed using SPSS 13.0 (SPSS Inc., USA). Statistical significance, determined by one-way ANOVA, was set at $P<0.05$. Data presented in graphs are expressed as mean±SD.

RESULTS

Immunoblot Analysis of NR2B

The NR2B in hippocampal extracts from rats was examined by quantitative immunoblot analysis and expressed as signal intensities of their bands. The results showed that the NR2B expression level was 0.61-fold higher in noise exposure group than in control group ($P<0.05$), suggesting that chronic noise exposure can lead to aberrant expression of NR2B containing NMDAR in hippocampus of rats (Figure 1).

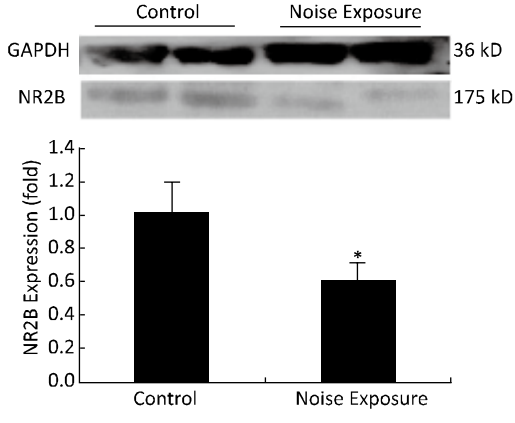

Figure 1. Western blott showing NR2B expression in rat hippocampus after chronic noise exposure. GAPDH was used as the internal reference protein, the quantified density of immunoreactive bands was expressed as percent of change relative to control samples, bars represent mean±SD, $^{*}P<0.05$ *vs* controls.

P-Tau Immunoreactivity

Changes in tau phosphorylation in hippocampal extracts from rats were studied by quantitative immunoblot analysis and expressed as signal intensities of their bands. The immunoactivity of p-Tau at Thr205 was 3.68-fold higher in noise exposure group than in control group ($P=0.0001$), indicating that chronic noise exposure may cause tau hyperphosphorylation at Thr205 in hippocampus of

rats (Figure 2).

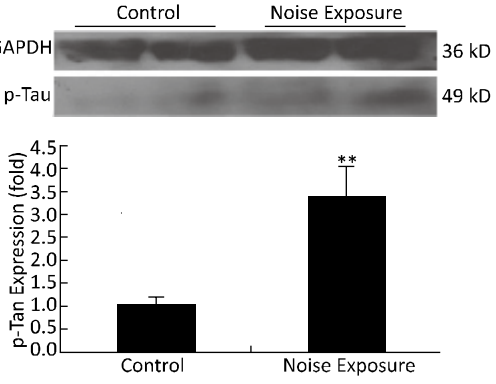

Figure 2. Western blot showing expression of p-tau in rat hippocampus after chronic noise exposure. GAPDH was used as the internal reference protein, the quantified density of immunoreactive bands was expressed as percent of changes relative to control samples, bars represent mean±SD, $^{**}P<0.01$ *vs* control samples.

To supplement results obtained by Weston blot and to further investigate the spatial distribution patterns of tau phosphorylation, hippocampus from both groups was examined with immunohistochemistry. The p-Tau (Thr205) immunopositive signals were expressed as DG, CA1, and CA3 with very weak staining in hippocampus of control group (Figure 3 A, B, C). The p-Tau (Thr205) immunopositive matter in hippocampus was expressed more significantly in CA1-3 pyramidal cell layer and DG granule cells of chronic noise exposure group than in control group (CA1: 0.56±0.05 *vs* 0.19±0.02, $P<0.01$; CA3: 0.62±0.06 *vs* 0.23±0.03, $P<0.01$; DG: 0.66±0.08 *vs* 0.24±0.04, $P<0.01$. as shown in Figure 3 A1, B1, C1, and Figure 4). Thus, our immunohistochemical staining results were consistent with the immunoblotting results.

TUNEL Staining

No TUNEL positive cells were found in control group (Figure 5 A-C). TUNEL-positive neurons were observed in CA1-3 pyramidal cell layer and DG granule cells (Figure 5 A1-C1). The TUNEL-positive neurons were estimated to constitute 0.5%-1% of the total neurons.

DISCUSSION

Effects of long-term noise exposure which do not habituate but increase long-term risk of physical damage are assessed as health hazards[20]. It was demonstrated that chronic noise exposure causes aberrant changes in the glutamate neurotransmitter system, including Glu and its NMDA receptor, GABA, and cognition deficit and that NR2B expression, tau hyperphosphorylation and neural apoptosis decrease in hippocampus after chronic noise exposure[7], indicating that abnormality of the neurotransmitter system, especially Glu and NR2B-containing NMDA receptor, and tau hyperphosphorylation in hippocampus, may play a role in chronic noise-induced neural apoptosis and cognition impairment.

EAA neurotoxicity is predominantly mediated by Glu receptors[21]. NMDAR exhibits a higher permeability for Ca^{2+} than for AMPA or KA receptors, possesses a higher ability to induce intracellular Ca^{2+} overload and initiates degenerative cascade[22], and mediates opposing effects according to their localization. Stimulation of synaptic NMDAR induces prosurvival events, whereas activation of extrasynaptic NMDAR leads to excitotoxic death[23]. It was reported that NR2A containing NMDARs is predominantly confined to synapses, whereas NR2B containing NMDARs is particularly distributed in extrasynaptase[13]. In this study, the expression of NR2B deceased significantly in hippocampus. However, its relevant mechanism was not completely clear yet. One of the reasons may be the loss of neurons.

Stressors, such as food deprivation, cold water swimming and ether anesthesia, cause Alzheimer-like progressive tau hyperphosphorylation in brain[17-18,24-25]. Acute stress reversibly increases soluble tau phosphorylated in mouse brain, whereas chronic stress induces both soluble and insoluble tau phosphorylated[26], indicating that chronic stress may be more harmful than acute stress. Tau hyperphosphorylation is usually most prominent in hippocampus, which is associated with the initial AD neuropathology[27-28]. Thr205 is one of the major sites on tau protein that is highly phosphorylated in AD brain[29]. In this study, tau was hyperphosphorylated after chronic noise exposure, which is directly related to cognitive impairment and neurodegeneration[30]. Psychological distress is not only a risk factor for AD, but also a risk factor for memory impairment in AD patients[31-32]. It was reported that extra-synaptic NR2B containing NMDARs mediates tau hyperphosphorylation[33]. Noise-induced abnormality of the EAA-NMDAR signaling system is involved in tau hyperphosphorylation as over-activation of this signaling pathway

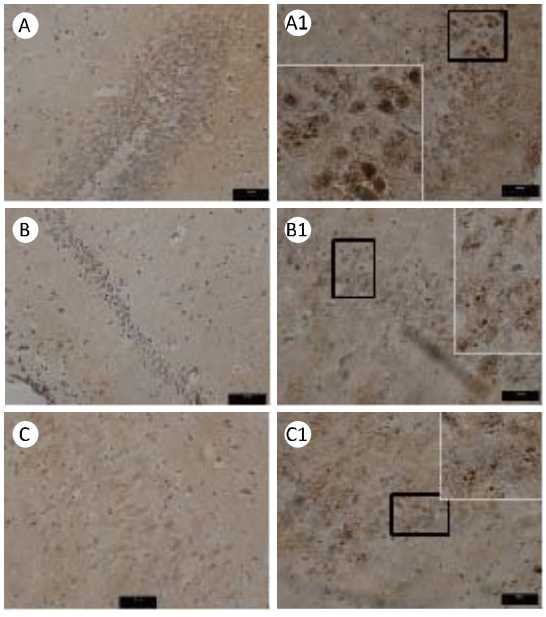

Figure 3. Immunohistochemical staining showing p-tau (Thr205) expression in hippocampus DG (A, A1), CA1 (B, B1), and CA3 regions (C, C1) of control group (A-C) and chronic noise exposure group (A1-C1). Boxed areas are shown in inserted pictures, bar=50 μm.

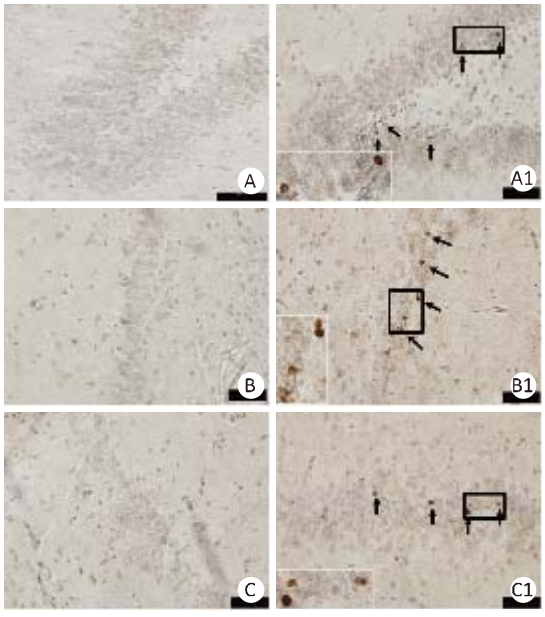

Figure 5. TUNEL immunoreactivity in hippocampus DG (A, A1), CA1 (B, B1), and CA3 regions (C, C1) of control group (A-C) and chronic noise exposure group (A1-C1). Arrows indicate surface in control group (A). Boxed areas are shown in inserted pictures. Bar=50 μm.

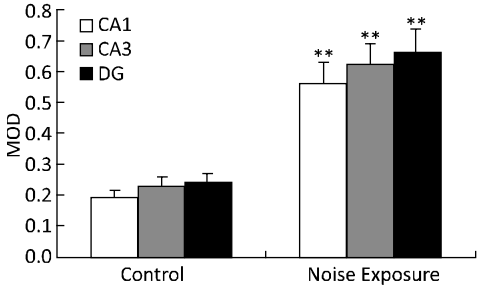

Figure 4. Immunoreactivity density of immunohistochemical staining of p-tau (Thr205). Bars represent mean±SD, $^{**}P<0.01$ *vs* controls.

enhances kinase activity[18,34-35]. More conspicuous tau hyperphosphorylation has been notably observed at Ser202/Thr205 (AT8 site) and Thr231/Ser235 among the prominently phosphorylated sites of PHF-tau in AD brains[29]. Accordingly, chronic noise exposure, as a cacoethic stressor, may also cause tau hyperphosphorylation at Ser202/Thr205 or Thr231/Ser235.

Neuronal apoptosis is characterized by neurodegenerative diseases[36] and ischemia[37-38]. Irrespective of the involved cell type, the hallmark of apoptosis is internucleosomal DNA degradation mediated by Ca^{2+}/Mg^{2+}–dependent endonuclease[39]. In this study, TUNEL-positive neurons were observed in hippocampus after chronic noise exposure, suggesting that chronic noise exposure exerts a deleterious effect on the neurons. It was reported that tau expression promotes neuronal apoptosis by activating the JNK pathway[40]. The apoptotic cells may be resulted from abnormality of the Glu-NMDAR system and tau hyperphosphorylation, which in turn lead to neurocognitive deficit.

Further studies are needed to fully understand the dose-effect relationship between noise exposure and its effect on CNS, and the physiological significance of tau phosphorylation in brain upon noise exposure. It was reported that tau is hyperphosphorylated in rat hippocampus for at least 24 h after acute noise exposure[41]. Pathological agent needs to be further investigated, hoping that further insights into the molecular consequences after noise exposure in brain would shed important light on intriguing correspondence in cognitive impairment on the one hand and noise-related molecular neural abnormalities on the other.

In conclusion, chronic noise exposure decreases

NR2B expression, tau hyperphosphorylation and apoptosis in hippocampus. Decreased NR2B expression may be related with apoptosis-induced loss of neurons. However, further study is needed to clarify their causal relationship.

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