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RESEARCH

The Role of Histone H2B Acetylation Modification in Aluminum-Induced Cognitive Dysfunction

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Abstract

Aluminum (Al) is a low toxic trace element that can accumulate in the nervous system and induce cognitive disorders characterized by reduced learning and memory ability. Neuroepigenetic effects are structural changes in cellular function by the brain in response to environmental stimuli by altering the expression of specific genes and repressing normal cellular transcription, leading to abnormalities in a variety of biological processes within the nervous system and affecting neurobehavioral responses. One of the most important mechanisms of epigenetic control on chromatin shape is histone modification. In the present study, we established an offspring rat model of Al intoxication to investigate the changes in spatial learning and memory retention abilities and the relationship with histone H2B acetylation modification in rats exposed to different doses of Al over a long period of time. The results demonstrated that long-term $AlCl_3$ staining resulted in decreased CBP gene and protein expression, increased HDAC3 gene and protein levels, as well as decreased histone H2B and acH2BK20 protein expression levels in the hippocampus of rats. In conclusion, long-term exposure to Al may vary the expression of histone H2B and acH2BK20 through the regulation of enzymes that specifically regulate histone acetylation, hence hastening the deterioration of the nervous system that impairs cognitive function.

Keywords $AlCl_3$ · Histone acetylation · Histone H2B · CBP · HDAC3 · Cognitive dysfunction

Introduction

As we all know, aluminum (Al) is a metalloid not just a mental. Several studies have demonstrated the impact of Al on human health, and evaluating the relevance of measuring Al^{3+} levels to health is critical in medicine [21]. Currently, exposure to metal pollutants has become a serious public health problem worldwide, and Al serves as one of the potentially toxic metals. It has been demonstrated that Al cannot be fully metabolized and cleared by the human body, and long-term exposure can lead to an increased Al load in the human body over time [24]. The neurotoxic effects of chronic Al overdose have been widely demonstrated. Blood Al levels exceeding 100 μg/L cause Al toxic effects, and urinary Al concentration reaching 100 μg/L is considered to be the critical concentration for the development of neurological complications [20]. Studies [5] have shown that even a "tolerable" dose of Al intake increases the level of Al ions in the nervous system, posing a neurological threat through biochemical imbalances and neurochemical alterations in the neurological parenchyma leading to damage in areas of the brain that shape cognitive function.

Although Al is neurotoxic, its toxicity mechanisms are poorly understood, and there are few well-defined mechanisms to describe these processes. Recent studies [9] have shown that the molecular effects of exogenous substances go far beyond interactions with DNA sequences, and that exogenous environmental pollutants can alter genomic function in the absence of changes in DNA sequences.

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Neuroepigenetic effects are structural changes in cellular function by the brain in response to environmental stimuli by altering the expression of specific genes and inhibiting normal cellular transcription [14], which can lead to abnormalities in a variety of biological processes within the nervous system and affect neurobehavioral responses [25]. Post-translation modifications (PTMs) are a key mechanism for epigenetic regulation of chromatin structure, which is known as the "histone code" [4]. The types of modifications on histones, including acetylation, methylation, phosphorylation, ubiquitination, and glycosylation, affect gene transcription, translation, and regulation mainly by altering chromatin structure [17].

Histone acetylation occurs mainly on lysine residues at the amino acid termini of core histones, dynamically reversible and tightly regulated histone modifications that are associated with active transcription [19] and regulate plasticity and memory processes. A specific increase in H2B acetylation in the dorsal hippocampus of rats was found during the memory consolidation phase [3]. Histone H2B undergoes acetylation modifications mainly at Lys5, 12, 15, 16, and 20. Among them, histone acH2BK20 has a unique role in the cis-regulation of specific gene expression as well as in specific biological functions [13]. Histone acetylation is carried out by histone acetyltransferases (HATs), including CBP (CREB-binding protein), p300, GCN5, PCAF (p300/CBP-binding factor), Tip60, and MOF (no males in species 12) [22]. Histone deacetylation is catalyzed by histone deacetylase (HDAC), which is divided into four classes: class I (HDAC2, 3, 8, and 4), class II (HDAC5, 6, 7, 9, 10, and 1), class III (Sirt7-11), and class IV (HDAC13) [23]. Interestingly, a recent study showed that both HAT and HDAC are associated with transcriptionally active genes occupied by RNA pol II, suggesting that HAT and HDAC dynamically control transcription by adding or removing acetyl groups to target histones, respectively [26]. CBP, one of the most widely studied HATs in the brain, is a key part of a specific network composed of multiple transcription factors and exogenous signals that direct neuronal cell fate during growth and development [12]. It has been shown that CBP is essential for the in vivo acetylation of lysine on histone H2B, and that loss of CBP in the dorsal CA1 region of the hippocampus leads to long-term enhancement of situational fear and object recognition and selective impairment of long-term memory [2]. Learning and memory deficits can be attenuated by blocking deacetylation through the application of drugs targeting inhibition of HDAC activity, among which, HDAC3 inhibitors rescued fear conditioning and new object recognition deficits induced by mutations in CBP [10]. HDAC3 acts as a negative regulator of learning and memory, and mice with loss of HDAC3 in the hippocampus showed improvement in long-term memory when tested on object recognition tasks [16].

Al may affect cognitive function because it is an external metal ion. Nevertheless, there have been no published investigations on how H2B acetylation alteration affects gene expression and the response to surrounding Al exposure. Since the Al that laboratory animals consume through food or drink is comparable to the Al that people actually consume, we used Al-containing drinking water to establish animal models of cognitive impairment. Based on the above, the present study took histone H2B acetylation as a breakthrough point to analyze whether the neurobehavioral abnormalities and impaired learning and memory functions in growing rats in the background of Al exposure were associated with H2B histone acetylation modification, aiming to provide theoretical references for the prevention of Al poisoning.

Materials and Methods

Animal Models

Forty female and 20 male Wistar rats with SPF-grade were purchased from Liaoning Changsheng Biotechnology Co. Ltd (Animal Qualification Certificate No. SYXK (Liao) 2019–0005). Rats were fed with rat food, and the feed was purchased from Shenyang Qianmin Feed Co., LTD. Rat food's primary components include imported fish meal, imported chicken meal, soybean meal, corn, meat and bone meal, broken rice, and other carefully chosen materials. It is devoid of antibiotics and medications, and its health indicators satisfy national requirements. Acclimatization feeding was performed for 7 days in 2:1 co-cages, and after conception, the pregnant rats were randomly divided into a control group (distilled water) and three $AlCl_3$-contaminated groups (2.0 g/L, 4.0 g/L, and 8.0 g/L), according to random number table method and according to body weight, with 10 rats in each group. Neonatal rats suckled breast milk and ingested Al before weaning, and drank water on their own after weaning, and were continuously poisoned for 90 days. The rearing environment and feed water met the requirements of no aluminization, providing standard rearing conditions (indoor constant temperature and humidity, 12-h day and night cycle), free feeding, and drinking. All subsequent experiments were conducted on randomly selected rats and each experiment was repeated three times.

The feeding and operation process followed the regulations of animal experiment management of Shenyang Medical College, and the experimental procedures were approved by the Laboratory Animal Research Center and Institutional Ethics Committee of Shenyang Medical College (Ethical Review No.: SYXY2021021402).

The preparation of $AlCl_3$ solutions was described in our previous publication [15].

Morris Water Maze Experiment (MWM)

The MWM experiment was utilized in this study to investigate the rat's capacity for spatial learning and memory. In the localization and navigation phase, each rat localized the hidden platform from four entry points four times a day for 5 days. In the spatial exploration phase, the platform was removed, and rats were allowed to swim freely for 30 s after entering the water from the farthest point of the platform. The swim trajectory system (Stoeling, USA) was recorded to automatically count escape latency, the number of times the platform was traversed, and the time spent in the target quadrant.

Dissociation of Hippocampus

After behavioral testing, 10% chloral hydrate (intraperitoneal injection, 0.3 mL/100 g) was given for euthanasia. Brain tissue was placed on ice for rapid dissection and removal, the tissue surface was rinsed with saline, and the bilateral hippocampus was removed by forceps stripping and stored in a refrigerator at − 80 °C.

Determination of Al^{3+} in Hippocampus

Al^{3+} concentration in rat hippocampus was detected by inductively coupled plasma mass spectrometry (ICP-MS) using the method described in previous literature [6].

Observation of Ultrastructure of Neurons in CA3 Region of Hippocampus

Images of hippocampal neurons were collected by transmission electron microscopy under photographic observation, as described in the methodology of a previous study [6].

Real-Time PCR Analysis

Real-time fluorescence quantitative PCR was used to analyze the expression levels of CBP and HDAC3 genes. Total RNA was extracted from the samples using Monzol™ (Monad, China) reagent according to the instructions. The expression of CBP and HDAC3 was detected using PrimeScript one-step RT-PCR kit (Takara, China). Equal mass cycling index values were measured for each sample, and the relative expression levels of target genes were calculated using the $2^{-\Delta\Delta Ct}$ method, with GAPDH as an internal reference.

Western Blotting Analysis

Western blotting was performed to analyze the protein expression levels of CBP, HDAC3, histone H2B, and acH2BK20. Protein samples were separated by gel electrophoresis and transferred to PVDF membrane. Primary antibodies were incubated with CBP (1:1000) (ABclonal, China), HDAC3 (1:2000) (ABclonal, China), H2B (1:5000) (Beyotime, China), acH2BK20 (1:1000) (PTM BIO, China), and β-actin (1:2000) (Proteintech, China); secondary antibody hybridization: the ratio was 1:5000. Chemiluminescent signals were detected using an ECL kit (Servicebio, China).

Statistical Analysis

Databases were created and statistically analyzed using EpiData 3.1 and SPSS 24.0. Correlation analysis was performed using Spearman correlation analysis. One-way analysis of variance (ANOVA), LSD analysis, or Dunnett's analysis were used to compare differences between groups. The experimental data were expressed as means ± SD, and a difference of $P < 0.05$ was considered statistically significant. $^{a}P < 0.05$; $^{b}P < 0.01$.

Results

Basic Condition of $AlCl_3$-Toxic Rats

There were no rat deaths in any of the groups during the contaminated period. The differences were not statistically significant ($P > 0.05$) when analyzed by the overall weekly water intake, food intake, and daily activity status of each group. The rats in the control group were in good condition, responsive, and had smooth and shiny fur. In the Al-tainted groups, the rats were basically in normal mood, with reduced activity and dull and disheveled fur, which was more obvious in the high-dose group.

Effects of $AlCl_3$ Tainting on the Growth and Development of Rats

As can be seen from Fig. 1, there was little difference in the body weights of the rats in each dose group at birth, and the body weights of the rats in each group increased with time. After 90 days of chronic Al intoxication, the body weights of the rats in the Al-intoxicated groups were lower than those of the control group ($P < 0.01$), indicating that continuous Al intake may lead to slow weight gain and possible growth retardation in rats.

Effect of $AlCl_3$ on Hippocampal Organ Coefficient

The hippocampal organ coefficient was calculated as: hippocampal organ coefficient = hippocampal weight (g) / body weight (g) × 100%. The hippocampal organ coefficients of rats gradually increased with the increase of toxicity dose, and all the $AlCl_3$-treated groups were elevated compared

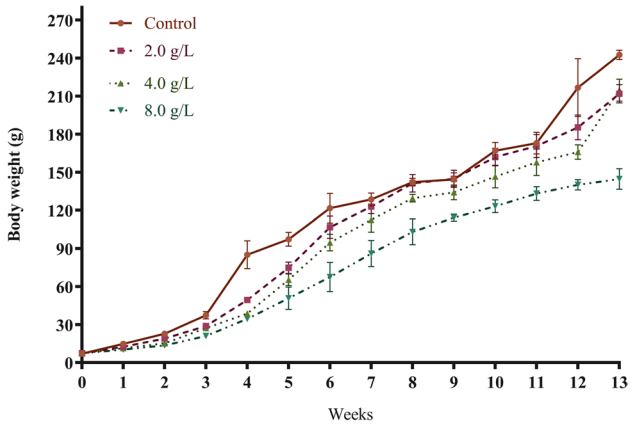

Fig. 1 Effects of $AlCl_3$ on growth and development of rats in each group ($N=8$)

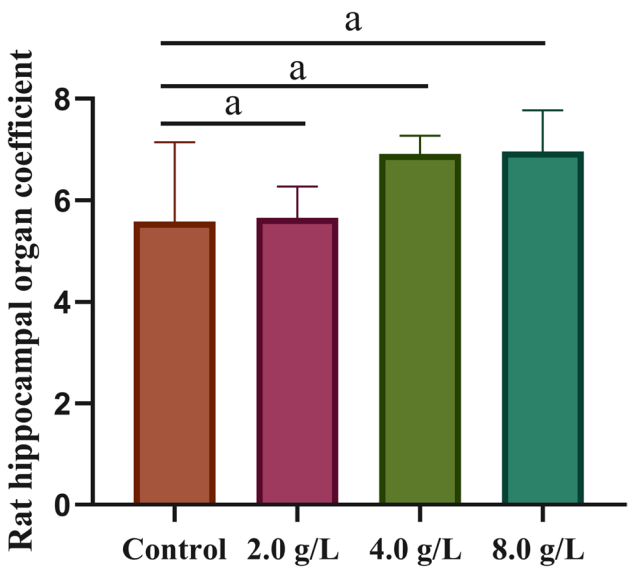

Fig. 2 Effect of $AlCl_3$ on hippocampal organ coefficient ($N=8$)

with the control group ($F=22.22$, $P<0.01$). Figure 2 shows that the hippocampal organ coefficients of the rats in the 2.0 g/L group were elevated compared with the control group, those in the 4.0 g/L group were elevated compared with those of the 2.0 g/L group, and those in the 8.0 g/L group were elevated compared with those of the other three groups.

Effects of $AlCl_3$ on Spatial Learning and Memory

The acquisition of spatial location and the retention of platform orientation memory in $AlCl_3$-contaminated rats were observed by the MWM test, and the results are shown in Fig. 3. The results of the fixed navigation test showed that the latency time of rats in the $AlCl_3$-contaminated group was elevated compared with that of the control group ($F=188,76$, $P<0.01$), which increased with the increase of the $AlCl_3$-contaminated dosage ($r=0.88$, $P<0.05$). Comparison between groups showed that the latency time of rats in the 4.0 g/L group was increased compared with the 2.0 g/L group, and the 8.0 g/L group was significantly increased compared with the 2.0 g/L and 4.0 g/L groups (Fig. 3A). Swimming path of rats in the Al-tainted group was elevated compared to the control group ($F=197.02$, $P<0.01$), which increased with the increase of Al-tainted dose ($r=0.87$, $P<0.05$). 4.0 g/L group increased compared to the control and 2.0 g/L groups, and the swimming path of the 8.0 g/L group increased compared to the other three groups (Fig. 3B).

The results of the spatial exploration test showed that the residence time and the number of traversals in the quadrant where the platform was located were negatively correlated with the Al dose in the Al-treated groups ($F=254.41$, $r=-0.87$, $P<0.05$; $F=144.07$, $r=-0.98$, $P<0.05$). Comparison between groups showed that the residence time in the target quadrant was lower in the 4.0 g/L and 8.0 g/L groups than in the 2.0 g/L group (Fig. 3C), and the number of traversals in the 8.0 g/L group was significantly lower than that in the 2.0 g/L and 4.0 g/L groups (Fig. 3D).

Effect of $AlCl_3$ on the Content of Al^{3+} in Hippocampus

Hippocampal $AlCl_3$ uptake was measured by ICP-MS as seen in Fig. 4. The Al^{3+} content in the Al intake group showed a gradual increase in uptake compared to the control group ($F=59.52$, $P<0.01$), which increased with increasing dose of $AlCl_3$ intake ($r=0.92$, $P<0.05$). The 4.0 g/L group showed an increase in Al^{3+} content compared to the control group, and the 8.0 g/L group showed an increase in $AlCl^{3+}$ content compared to the control and the 2.0 g/L group.

Effect of $AlCl_3$ on Ultrastructure of Hippocampal CA3 Region

The hippocampus is a sensitive area in the brain for shaping learning and memory, and its structure and function can be used as an important physiological basis for learning memory observables. The ultrastructural changes of neurons in the CA3 area of rat hippocampus were observed by transillumination (Fig. 5). The neurons in the control group were basically normal in shape, rounded, with uniform chromatin distribution in the nucleus, and the neurons in the $AlCl_3$-stained neurons showed different degrees of atrophy and deformation, with elliptical or irregular shapes, contraction of the cell membrane, and aggregation of

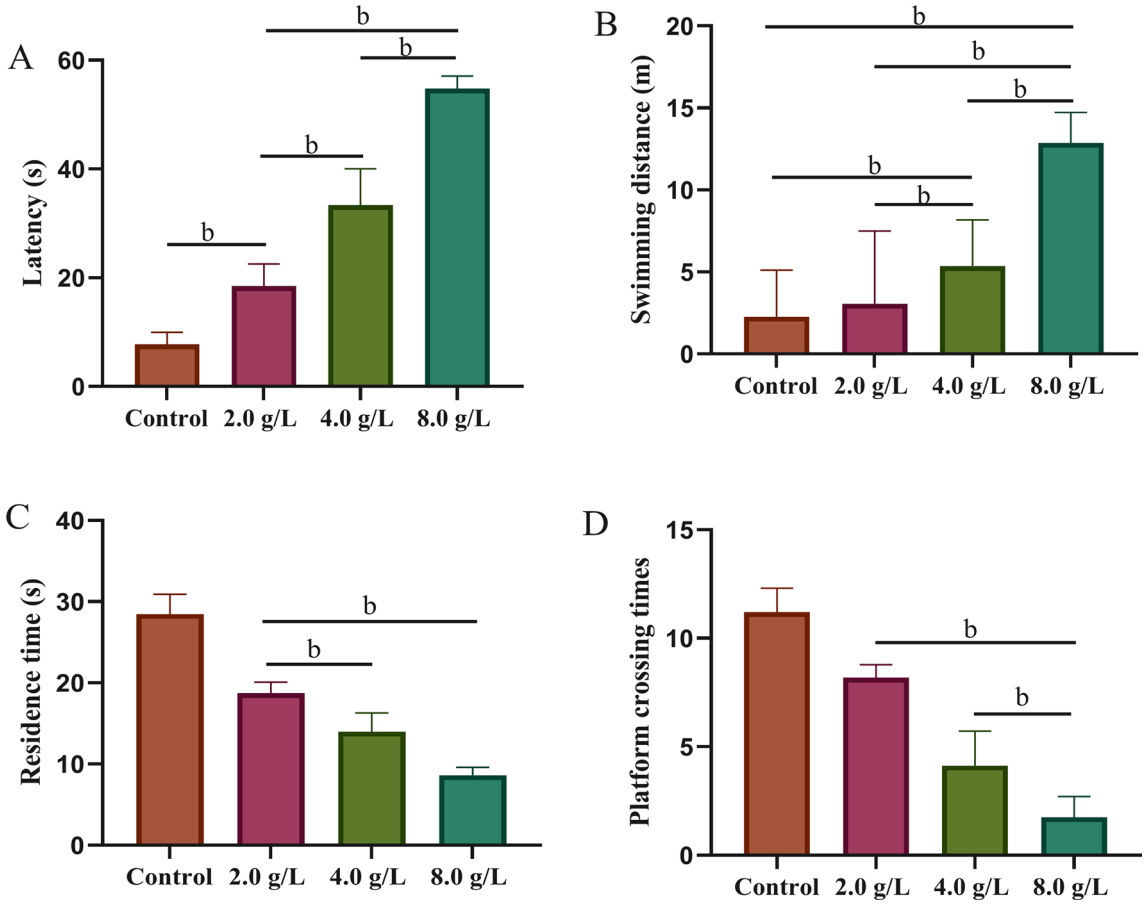

Fig. 3 Effects of $AlCl_3$ on spatial learning and memory ($N=8$)

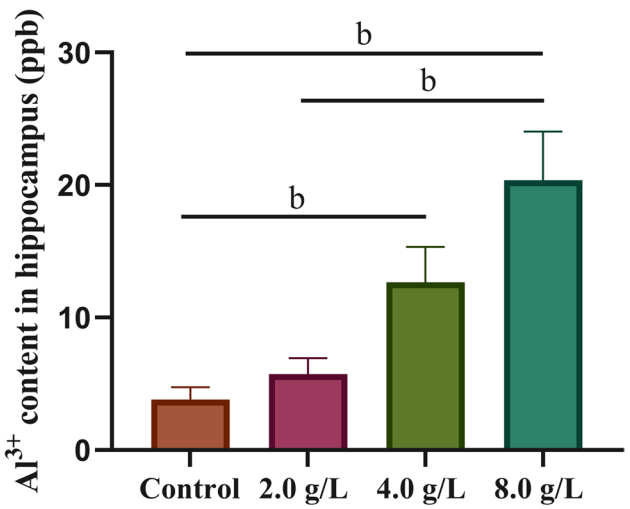

Fig. 4 Effect of $AlCl_3$ on the content of Al^{3+} in hippocampus ($N=8$)

heterochromatin, which worsened with increasing dosages of $AlCl_3$ staining. The above damage was aggravated with the increase of $AlCl_3$ dose.

Effect of $AlCl_3$ on the Expression of CBP and HDAC3 mRNA

CBP is the specific histone acetyltransferase for hippocampal-dependent learning memory, and its expression level was determined by RT-PCR, and the results are shown in Fig. 6. The expression level of CBP mRNA decreased with the increase of tainted dosage ($F=13.59$, $r=-0.74$, $P<0.05$); the opposite was true for HDAC3 ($F=8.57$, $r=-0.48$, $P<0.05$). The expression level of CBP mRNA of the 4.0 g/L and 8.0 g/L groups had significantly lower CBP mRNA expression levels than the control group (Fig. 6A). HDAC3 mRNA expression levels of the 8.0 g/L group were increased compared with the control, 2.0 g/L, and 4.0 g/L groups (Fig. 6B).

Effect of $AlCl_3$ on Histone CBP, HDAC3, H2B, and acH2BK20 Protein Content

As shown in Fig. 7, CBP, H2B, and acH2BK20 protein contents in the hippocampal tissues of rats in the Al-stained group decreased with increasing doses of

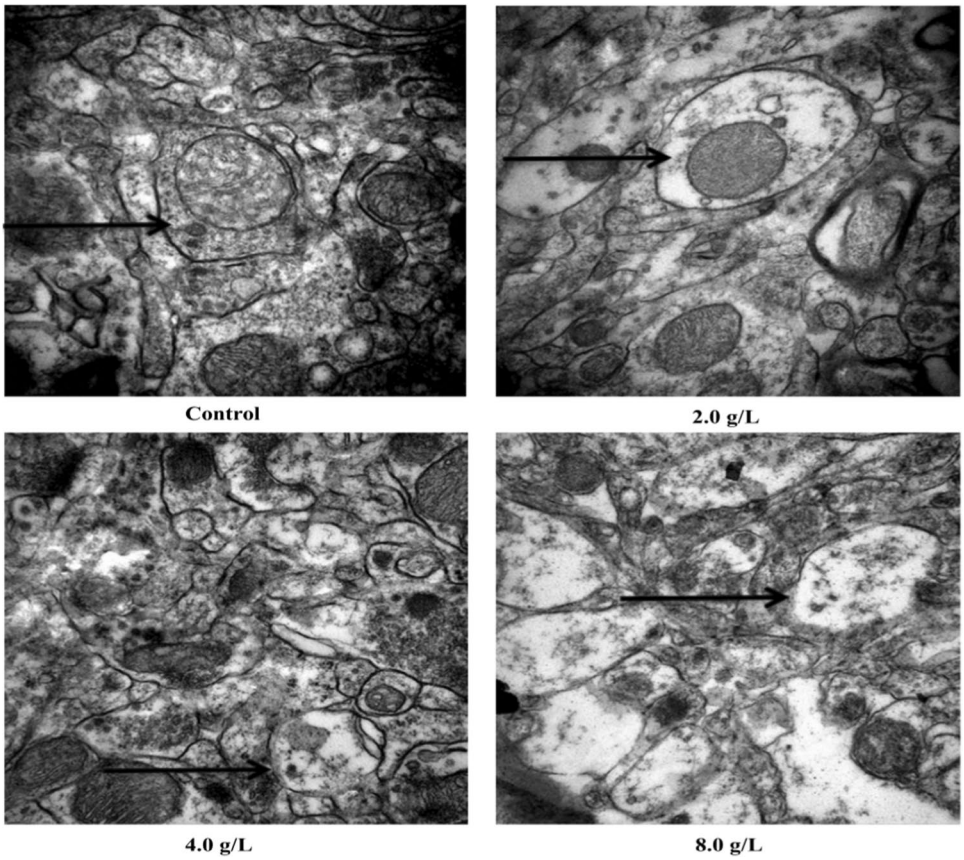

Fig. 5 Effect of $AlCl_3$ on ultrastructure of hippocampal CA3 region (magnification: 50 K, $N=8$)

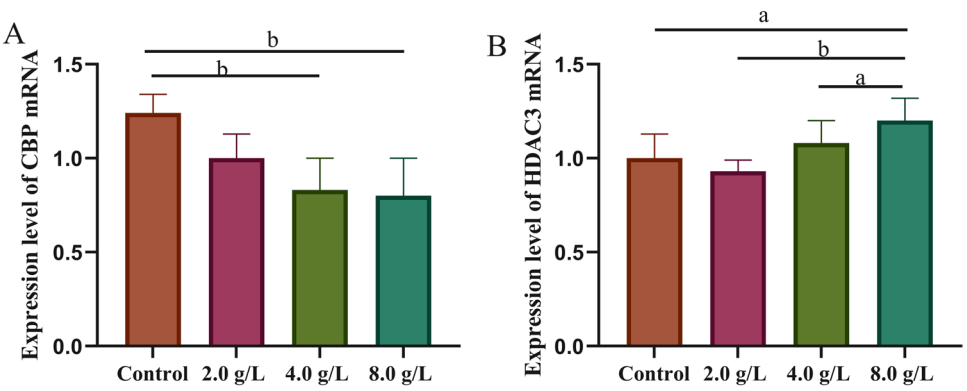

Fig. 6 Effect of $AlCl_3$ on the expression of CBP and HDAC3 mRNA in hippocampus ($N=8$)

$AlCl_3$ staining ($F=6.48$, $r=-0.63$, $P<0.05$; $F=34.53$, $r=-0.89$, $P<0.05$; $F=3.36$, $r=-0.50$, $P<0.05$); the opposite was true of HDAC3 ($F=5.47$, $r=0.48$, $P<0.05$).

Comparison between groups showed that CBP protein content was decreased in the 2.0 g/L and 4.0 g/L groups compared with the control group. CBP protein content was decreased in the 4.0 g/L group compared with the control and 4.0 g/L groups (Fig. 7A). HDAC3 protein content was elevated in the 2.0 g/L group compared with the control group, and in the 4.0 g/L group compared with the control and 2.0 g/L groups, and the 8.0 g/L group was significantly elevated compared with the other three groups (Fig. 7B). H2B protein content in 8.0 g/L group was decreased compared to the control and 2.0 g/L group (Fig. 7C). acH2BK20 protein content in the 4.0 g/L group was decreased compared to the control, 2.0 g/L, and 8.0 g/L group; acH2BK20 protein content was reduced compared to the other three groups (Fig. 7D).

Discussion

Exposure to Al ions in a form that is correlated with the acidity values in the surrounding environment is what is known as Al toxicity, Al in drinking water exists in a

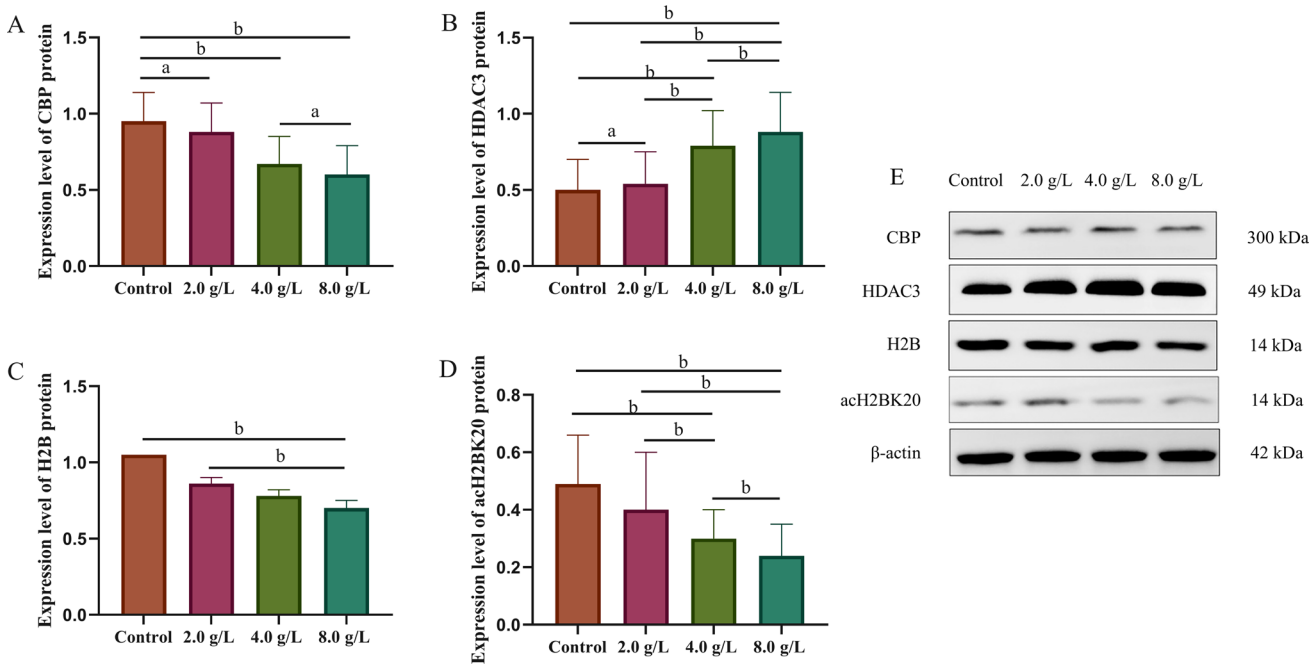

Fig. 7 Effect of $AlCl_3$ on histone CBP, HDAC3, H2B, and acH2BK20 protein content in hippocampus ($N=6$)

free form with a small particle size, and the amount of Al absorbed from water intake (about 0.3%) is greater than that absorbed from food (about 0.1%) [8]. When Al enters the body, it is absorbed slowly under physiological pH settings. However, in acidic environments, like the gastrointestinal tract, it can stimulate its release, which causes a tenfold increase in absorption. In the present study, we simulated Al metabolism in humans by drinking water, and showed that gastrointestinal toxicity in rats within 90 days of birth can directly lead to the accumulation of Al^{3+} in the body, which crosses the physiological barrier and is overloaded in the nervous system. The toxicological effects of Al are widespread in all organs and accumulate throughout the life course, from early development to adulthood. In this study, $AlCl_3$ tainting started from the first day of life until day 90 in rats, simulating $AlCl_3$ exposure from infancy to adulthood. It was shown that with the accumulation of time, among all groups exposed to different doses of $AlCl_3$, delayed weight gain and growth retardation were observed in the Al-stained group, which is consistent with the previous study [15]. This suggests that there is a dose–effect relationship between Al exposure and growth and development, and that early Al exposure may have long-lasting irreversible consequences on development.

In exploring neurotoxicity, the hippocampus is an important target for studying changes in cellular and molecular mechanisms related to learning and memory. Nampoothiri demonstrated [18] that the concentration of Al accumulation in hippocampal tissues is higher than that in other brain regions such as the cortex and amygdala. When long-term Al accumulation is presented, the hippocampus is damaged, and learning and memory functions appear to be altered accordingly [28]. Additionally, our research demonstrated that the hippocampus is specifically home to Al and that long-term exposure to Al at varying concentrations led to the build-up of Al^{3+} in the hippocampus, which in turn caused abnormalities in the hippocampus's ultrastructure and function. However, the exact location of Al deposition in other brain regions, such as the amygdala and cortical layers, and its impact on the related functions need to be further verified and investigated in detail. Al content can be detected by indicators such as hair, urine, and blood, but it is generally difficult to notice Al toxicity, which is often detected through external behavioral manifestations. In this study, the MWM experiment was chosen to assess the abnormal behavioral responses of Wistar rats under Al-tainted poisoning, and the results showed a significant correlation between brain Al loading and the potential risk of spatial learning and memory.

Histone acetylation is one of the most widely studied mechanisms of histone modification, and global histone acetylation measurements in the rat hippocampus during the early stages of spatial learning and fear memory formation have shown that H3, H4, and H2B undergo differential acetylation at specific localization sites, with H3K9 and K14 acetylation being able to respond to any experimental condition, and H2B N-terminal and H4K12 acetylation being primarily associated with memory for spatial or fear

learning [3]. Our research team has previously demonstrated that the level of H4 acetylation is reduced in the $AlCl_3$ background, accompanied by a decrease in the expression of site-specific H4K12 acetylation [6]. In the present study, H2B acetylation was used as the entry point to observe the changes in the expression of H2B and acH2BK20, and it was found that the expression of H2B decreased with the dose of tainted drug, and the trend of acH2BK20 was consistent with it. Therefore, we proposed that the diminished H2B and acH2BK20 expression might be associated with the rats' impaired learning and memory. Histone acetylation levels regulate gene transcriptional activity in response to HATs and HDACs. HAT promotes gene transcription and facilitates learning and memory,HDAC represses gene transcription and affects learning and memory. CBP is a specific HAT involved in learning and memory formation, and haploid-deficient mice show the presence of reduced acetylation, a defect in long-term enhancement of the hippocampus, and deficits in some forms of long-term memory; CBP's HAT activity-deficient mutants have spatially and temporally restricted expression, and these suggest the importance of CBP's HAT activity in hippocampus-dependent memory processes [1]. To further investigate the role of CBP in memory, based on a background of chronic Al staining of the hippocampus, we found that the level of CBP gene expression decreased with increasing doses of Al staining. It was shown [27] that CBP deletion leaves upstream signaling events intact, as evidenced by unchanged CREB phosphorylation, but can disrupt downstream events, such as the level of histone acetylation on multiple histones, as well as target c-fos expression and behavior. It remains to be further explored the mechanisms by which CBP modulates specific gene regulation during memory formation under Al neurotoxic effects. McQuown [16] observed that HDAC3-modified mice (deletion of HDAC1 in the CA3 region of the hippocampus) or mice treated with a selective inhibitor of HADC3 increased histone acetylation and significantly increased cognate and c-fos expression. Our group has previously found that HDAC1 is upregulated in Al staining, and the present study, like the previous findings, showed that HDAC3 expression and content in Al-stained rats increased with increasing doses of staining. Histone HDACs have 18 enzymes, among which HDAC3 is highly expressed in the brain and can form a neurotoxic complex with HDAC1, which produces neuroprotection by maintaining genetic stability. It has been analyzed [11] that the functions of different HDACs are interrelated, with HDAC1 being protective when interacting with HDAC9 and neurodamaging when interacting with HDAC3. Therefore, whether there are other HDACs regulated by HDAC3 for histone H2B regulation remains to be investigated.

The mechanism of neurotoxicity caused by Al is complex and diverse, not only acting on hippocampus cells; studies have also found that Al caused glial cell activation, sensitized DDX3X-NLRP3 pyroptosis pathway, released cytokines IL-1β and IL-18, and caused neuroinflammation [7]. Thus, environmental factors and life experiences can influence computerized circuits and trigger adaptive changes. Epigenetic regulators promote neural adaptation by enhancing or suppressing specific genetic programs. Further exploration of understanding Al as an environmental disruptor can help us better understand how organisms are susceptible to environmental toxic signals like Al exposure and how the expression profiles of encoded genes are affected by it. This is because Al drives epigenetic changes in the context of neurodevelopment and synaptic plasticity, as well as from the perspective of histone H2B acetylation modification.

In summary, long-term $AlCl_3$ contamination can cause Al deposition in rat hippocampus, change the ultrastructure of neurons in the CA3 area, lead to the reduction of spatial learning ability and memory retention ability, reduce the expression of two specific enzymes, histone CBP and elevated HDAC3, and reduce the content of histone H2B and acetylation-specific site acH2BK20 proteins, which then participate in the hippocampal synaptic plasticity and stimulation of transcription, affecting cognitive functions.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12011-023-03959-8.

Author Contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [J.G], [W.L] and [N.H]. The first draft of the manuscript was written by [J.G], [J.P] and [L.Z]and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability All data generated or analyzed in this study are available from the corresponding author on reasonable request.

Declarations

Ethics Approval The research was carried out following the National Institutes of Health Guide for the Care and Use of Laboratory Animals standard. The experimental procedure was approved by the Experi-

mental Animal Research Center of Shenyang Medical College and the System Ethics Committee (ethics review number: SYXY2021021402).

Competing Interests The authors declare no competing interests.

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