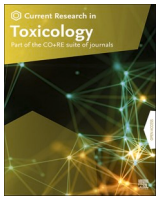
Current Research in Toxicology 7 (2024) 100193

Contents lists available at ScienceDirect

Current Research in Toxicology

journal homepage: www.journals.elsevier.com/current-research-in-toxicology



Research Paper

The role of TFEB-mediated autophagy-lysosome dysfunction in manganese neurotoxicity

Jiaqiao Lu [a,1], Peng Su [a,1], Fang Zhao [a], Kailun Yu [a], Xunbo Yang [a], Hui Lv [b], Diya Wang [a,*], Jianbin Zhang [a,*]

[a] Department of Occupational and Environmental Health, the Ministry of Education Key Lab of Hazard Assessment and Control in Special Operational Environment, School of Public Health, Fourth Military Medical University, No.169 Chang Le West Rd., Xi'an, Shaanxi 710032, China
[b] Department of Health Service Teaching and Research, Dalian Health Service Training Center of Chinese PLA, Da Lian 116001, China

ARTICLE INFO

Keywords:
Manganese neurotoxicity
Autophagy
Lysosome
TFEB

ABSTRACT

Excessive long-term manganese intake can inflict irreversible damage to the nervous system, with a predominant effect on the substantia nigra-striatum pathway. Through a mouse model simulating manganese exposure, we delved into its implications on the central nervous motor system, uncovering autophagy-lysosome dysfunction as a pivotal factor in manganese-induced neurotoxicity. Our research illuminated the molecular mechanisms behind TFEB's role in manganese-triggered neuronal autophagy dysfunction, offering insights into the cellular and molecular mechanisms of manganese-induced abnormal protein accumulation. This study lays a significant theoretical foundation for future endeavors aimed at safeguarding against manganese neurotoxicity. Furthermore, TFEB emerges as a potential early molecular biomarker for manganese exposure, providing a solid basis for preemptive protection and clinical treatment for populations exposed to manganese.

1. Introduction

Manganese is a naturally occurring mineral and one of the most abundant metal elements in mammalian tissues. However, long-term excessive manganese exposure can lead to toxicity in the body, primarily affecting the central nervous system (Erikson and Aschner, 2019; Mezzaroba et al., 2019). Neurological symptoms of manganese toxicity resemble Parkinson's disease and include gait imbalance, rigidity, tremors, and bradykinesia (Martins et al., 2019). Manganese neurotoxicity poses significant risks to occupational manganese-exposed workers (Lee et al., 2019; Dlamini et al., 2020). The mechanisms underlying this neurotoxicity remain unclear, with recent research focusing on dopamine depletion, the role of free radicals, mitochondrial damage, calcium homeostasis disruption (Ijomone et al., 2019), and abnormal protein accumulation (Tinkov et al., 2021; Yan and Xu, 2020). Increasing environmental pollution highlights the importance of studying chronic manganese toxicity, underscoring the widespread public interest and its implications for public health.

Autophagy is a critical cellular mechanism for preserving cell survival by clearing damaged or harmful cellular components, thus maintaining cellular homeostasis (Cao et al., 2021). During autophagy, target materials are engulfed by autophagosomes, which fuse with lysosomes to form mature autolysosomal structures, facilitating degradation by lysosomal proteases. Dysfunctional autophagy is associated with various diseases, including lung, liver, heart diseases, neurodegenerative disorders, myopathies, cancer, aging, and metabolic diseases (Levine and Kroemer, 2019). Dysregulated autophagy occurs in manganese neurotoxicity and plays a significant role (Ma et al., 2020) in the neurotoxic process (Yan and Xu, 2020). This is mainly because, in addition to the ubiquitin–proteasome system, the degradation of disease-associated mutant proteins heavily relies on the clearance function of autophagy (Vargas et al., 2023). Manganese exposure induces the oligomerization of alpha-synuclein continuously accumulating in the brain (Yan et al., 2019). Autophagic activation can protect neurons, delay, or ameliorate manganese neurotoxicity, although the specific mechanisms remain unclear (Zhang et al., 2020).

Lysosomes are organelles responsible for the degradation of large molecules within cells. They contain over 50 hydrolytic enzymes that degrade various cellular components, including proteins (Ballabio and Bonifacino, 2020; Zhang et al., 2021). Transcription factor EB (TFEB) is

* Corresponding authors.
E-mail addresses: dearyatt@yeah.net (D. Wang), zjbin777@fmmu.edu.cn (J. Zhang).
[1] Jiaqiao Lu and Peng Su contributed equally to this work.

https://doi.org/10.1016/j.crtox.2024.100193
Received 13 June 2024; Received in revised form 30 August 2024; Accepted 6 September 2024
Available online 11 September 2024

a major regulator of lysosomal biogenesis (Franco-Juárez et al., 2022). Studies have shown that TFEB overexpression enhances lysosomal and mitochondrial function, significantly reduces high-fat diet-induced hepatic steatosis in mice (Yan, 2022), and is closely associated with alcohol-induced hepatocyte death in a chronic alcoholism mouse model (Park et al., 2021). During manganese exposure, TFEB expression and its regulation of lysosomal function may also play a critical role in manganese neurotoxicity (Pajarillo et al., 2022).

The aim of this study was to investigate the role and mechanisms of TFEB-mediated autophagy-lysosome dysfunction in neuronal protein accumulation following manganese exposure. We found that manganese exposure led to decreased TFEB expression, disrupted autophagy-lysosome function, increased abnormal accumulation of alpha-synuclein, and enhanced Tau phosphorylation. Dysregulated autophagy mediated by TFEB may be a key factor in manganese-induced neuronal damage.

2. Materials and methods

2.1. Experimental animals, treatment, SN tissue collection

The Institutional Animal Care & Use Committee of the Fourth Military Medical University (FMMU) approved all experiments involving animals. Mice were housed in groups of up to 5 animals per cage with food and water provided ad libitum on a 12-hour light/dark cycle. Throughout the study we used C57/BL6 male mice weighting 20 ± 1 g. Mice were injected subcutaneously with manganese (II) chloride tetrahydrate ($MnCl_2$ $4H_2O$) in a subacute treatment based on a published protocol. Briefly, animals were randomly assigned to 2 treatment groups and injected with either 0.1 mL of $MnCl_2$ (100 mg/kg, in saline) and saline (0.9 % NaCl). This treatment was repeated every third day for a week, for a total of 3 treatments on 1, 4, and 7 d. The number of mice in each time point group was 12, and all mice used were male.

For SN (Substantia nigra) tissue collection following behavioral testing, the mice were killed by rapid cervical dislocation and brains were immediately removed and placed onto a chilled glass petri dish atop a bed of crushed ice. The brain was kept moist with phosphate-buffered saline (PBS; Sigma, P5493). The SN was dissected using microforceps and stored at −80 °C in 0.1 M PBS (pH 7.4).

2.2. Quantification of behavioral tests

Pole climbing test: Motor coordination was evaluated by crawling time of mice. A 2.5 cm diameter plastic ball is fixed on the top of a 50 cm × 1 cm cylindrical metal pole, and gauze is wrapped around the ball and metal pole to prevent slipping. The time required for mice to top down was recorded, tested 3 times, and the average was taken.

Open field experiment: The total distance and average speed of mouse activity reflected the autonomous motor ability. The tested mice were placed in the reaction box for 5 min, and their activities were collected using the tracking analysis system.

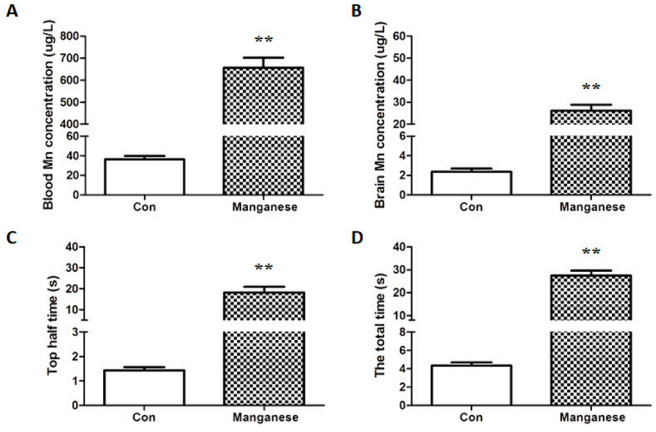


Fig. 1. Mn exposure leads to neurotoxicity. (A, B) Mn concentration in blood (A) and in brain (B) were determined by an atomic absorption spectrophotometer. Pole climbing test was used to measure the effect of Mn exposure on Motor coordination capacity in mice (C, D). The data were expressed as means ± SE of three independent experiments. **p < 0.01, compared with control group.

2.3. Manganese concentration analysis

At the end of the behavioral study, blood samples (0.1 ml) and brain samples (0.2 g) were collected from mice after decapitation in each group. The blood samples (0.1 ml/mouse) for measuring blood manganese levels were collected from the left ventricle. Manganese was extracted from brain tissues by drying them and digesting them with organic solubilizers. Manganese levels were measured in duplicate using a graphic furnace and an atomic absorption spectrometer (AAS) (PerkinElmer 600, USA).

2.4. Stereotaxic injection

A volume of 5×10^9 viral particles suspended in less than 250 nl of PBS was administered into the left SNc region using a stereotaxic apparatus (Stoelting, Wood Dale, IL) equipped with a pulled glass capillary needle (tip diameter < 50 μm) at the specified coordinates: AP: −3.2 mm, ML: −1.3 mm, and DV: −4.45 mm (Geibl et al., 2023). The injection was performed using a digital nanoinjector (Stoelting) connected to a mineral oil-filled 5-μl gas-tight syringe (Hamilton) over a duration of 5 min, with the syringe remaining in place for an additional 5 min post-injection. Subsequently, the syringe was removed, and the incision site was closed using cyanoacrylate glue (Vetbond, 3 M). The mice were administered ketoprofen for analgesia and monitored for signs of distress over a 48-hour period. This was followed by two days of convalescence, after which manganese treatment was initiated.

2.5. Transmission electron microscopy (TEM)

SNc tissues were immediately fixed in 2.5 % glutaraldehyde and dehydrated in ethanol. Processed tissues were then embedded in epoxy resin and sliced into 70 nm sections using an ultrathin slicer. After staining with uranyl acetate and lead citrate, morphological changes were captured and examined by a transmission electron microscope (Joel, JEM-2000EX, Tokyo, Japan).

2.6. Western blotting

Tissue lysates for western blotting were prepared as previously described. Briefly, lysis buffer was used to lyse brain tissue. Protein concentrations were measured using the bicinchoninic acid (BCA) protein assay kit (#P0010, Beyotime, China). Proteins were separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis and transferred to polyvinylidene fluoride membranes. After blocking membranes in skim milk, they were incubated overnight at 4 °C with primary antibodies. The following day, washed membranes were incubated with secondary antibodies. Protein bands were observed using enhanced chemiluminescent luminol and a chemiluminescence detector. Primary antibodies were: Tau-5 (21773-1-AP, Proteintech, 1:7,000), p-Tau396 (27260-1-AP, Proteintech, 1:3,000), α-syn(13050-1-AP, Proteintech, 1:5,000), Caspase 3 (66535-1-Ig, Proteintech, 1:4,000), Cathepsin D (3045S, Cell Signaling, 1:3,000), Cathepsin B (19655-1-AP, Proteintech, 1:5,000), β-actin (66009-1-Ig, Proteintech, 1:10,000), TFEB (12987-1-AP, Proteintech, 1:5,000). Beclin1(12987-1-AP, Proteintech, 1:5,000) and LC3 (12987-1-AP, Proteintech, 1:5,000).

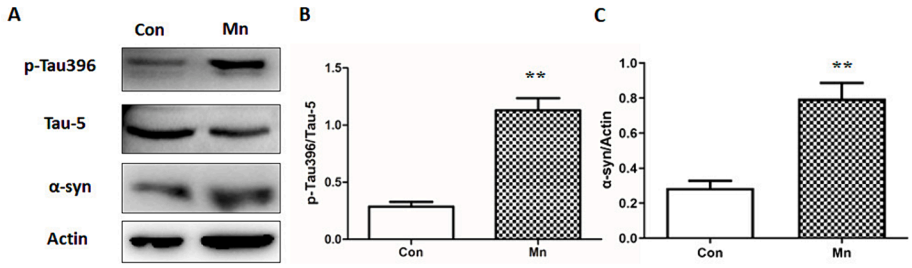


Fig. 2. Mn exposure leads to accumulation of abnormal proteins. The amounts of proteins (p-Tau396, Tau5, α-syn, and Actin) were monitored via Western blot analysis using the specified antibodies (A). Relative amounts of p-Tau396 (B) and α-syn (C) in panel. The data were expressed as means ± SE of three independent experiments. **p < 0.01, compared with control group.

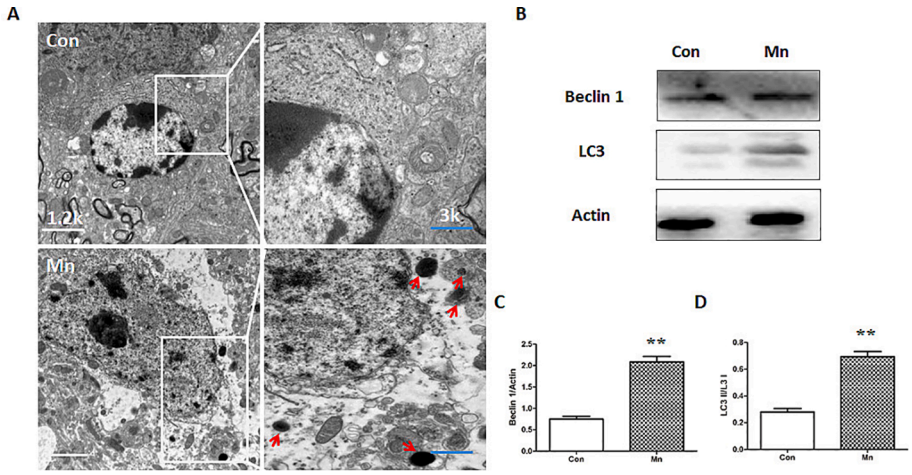


Fig. 3. Mn exposure could induce the accumulation of autolysosomes. After Mn exposure, autophagy body morphology in mice was observed under a high-resolution electron microscope (A). The amounts of proteins (Beclin 1, LC3 and Actin) were monitored via Western blot analysis using the specified antibodies (B). Relative amounts of Beclin 1 (B) and LC3 (C) in panel. **p < 0.01, compared with control group.

2.7. Statistical analysis

A minimum of three experiments were performed, and the results were expressed as means ± SEM. Post-hoc analysis was conducted using a two-way ANOVA followed by the Turkey test. Differences with p-values <0.05 were considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) 22.0 software (SPSS Inc. IL, USA). The specific indices of statistical significance were indicated in individual figure legends.

3. Results

3.1. Manganese exposure induces the accumulation of alpha-synuclein and phosphorylation of Tau protein

We established a subacute manganese exposure model by subcutaneously injecting $MnCl_2$. One week after $MnCl_2$ subcutaneous injections, blood and brain manganese levels significantly increased compared to the control group (Fig. 1A, B). Manganese exposure led to abnormal brain motor function in mice, as assessed by the pole-climbing test. Results showed that mice exposed to manganese spent significantly more time at the top and took longer to climb down compared to the control group (Fig. 1C, D). Manganese exposure affected mouse motor function. Western blot analysis of protein expression in dopaminergic neurons of the substantia nigra pars compacta revealed that manganese exposure increased Tau protein phosphorylation levels and alpha-synuclein expression levels compared to the control group (Fig. 2A).

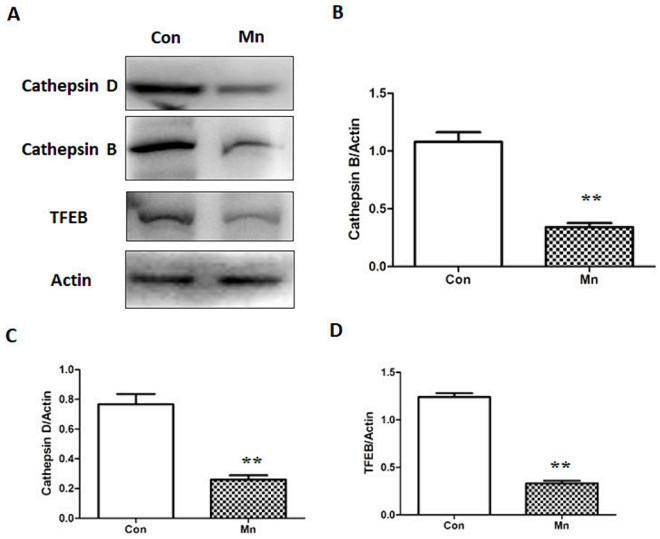


Fig. 4. Mn exposure leads to reduce the function of lysosomal. Protein expression of lysosomal function related proteins were examined by western blot (A). Relative amounts of Cathepsin D (B), Cathepsin B (C) and TFEB (D) in panel. The data were expressed as means ± SE of three independent experiments. **p < 0.01, compared with control group.

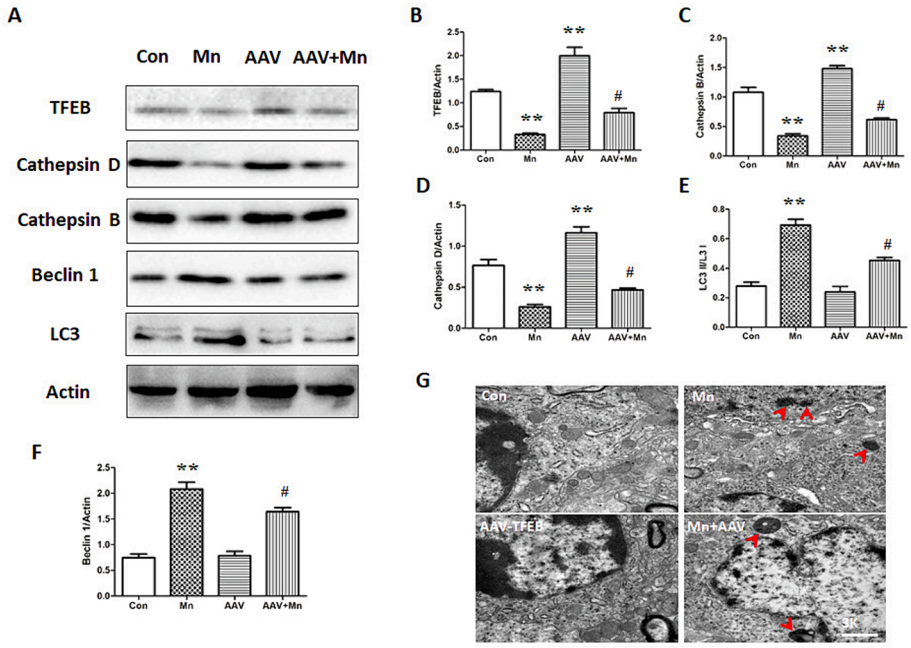


Fig. 5. Overexpression of TFEB can promote the function of autolysosome. C57BL6 mice were pretreated with AAV, promoting the expression of TFEB, and then exposed to Mn. Protein expression of lysosomal function related proteins were examined by western blot (A). Relative amounts of TFEB D (B), Cathepsin B (C), Cathepsin D (D), LC3 II (E) and Beclin 1 (F) in panel. Autophagy body in mice was observed under a high-resolution electron microscope (G). The data were expressed as means ± SE of three independent experiments. **p < 0.01, compared with control group, #p < 0.05, compared with Mn-treating group.

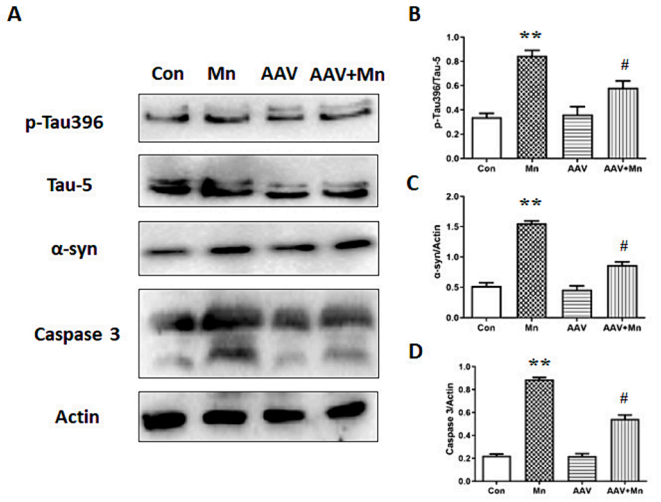


Fig. 6. Over expression of TFEB can reduce the abnormal protein folding and accumulation in neurons. The amounts of proteins (p-Tau396, Tau5, α-syn, Caspase 3 and Actin) were monitored via Western blot analysis using the specified antibodies (A). Relative amounts of p-Tau396 (B) α-syn (C) and Caspase 3(D) in panel. The data were expressed as means ± SE of three independent experiments. **p < 0.01, compared with control group, #p < 0.05, compared with Mn-treating group.

3.2. Manganese exposure impairs autophagic function

Transmission electron microscopy was used to observe changes in autophagosomes in dopaminergic neurons of the substantia nigra. Results showed that manganese exposure increased the number of autophagic vesicles within neurons, and lysosome degradation was impaired (Fig. 3A). Western blot analysis of autophagy-related proteins revealed that manganese exposure promoted the expression of Beclin 1 and LC3II, indicating enhanced autophagy formation (Fig. 3B). However, autophagosomes remained in an undegraded state.

3.3. Manganese exposure suppresses TFEB expression and lysosomal degradation function

TFEB is a crucial regulator of lysosome biogenesis and maintenance of its function. Manganese exposure inhibited TFEB expression in nigral neurons (Fig. 4A). Manganese exposure suppressed lysosome biogenesis and normal function. Western blot analysis of lysosomal proteases D and B revealed that manganese exposure inhibited the expression of lysosomal proteases (Fig. 4A). The number and function of lysosomes were both affected by manganese exposure.

3.4. TFEB overexpression alleviates autophagy-lysosome dysfunction

We constructed an adeno-associated virus (AAV) expressing TFEB and stereotaxically injected it into the substantia nigra of mice. Experimental verification showed that AAV viral injection increased TFEB protein expression in the substantia nigra. After TFEB overexpression, manganese exposure improved lysosomal protease expression (Fig. 5B), increased lysosome generation, and enhanced lysosomal function. The number of autophagosomes in neurons significantly decreased after TFEB overexpression, effectively alleviating manganese-induced autophagy-lysosome dysfunction.Fig. 6.

3.5. TFEB overexpression reduces manganese-induced Tau protein over phosphorylation and abnormal accumulation of alpha-synuclein

Western blot analysis of the substantia nigra showed that TFEB overexpression effectively suppressed manganese-induced Tau protein phosphorylation and alpha-synuclein accumulation. TFEB may regulate abnormal protein accumulation in neurons by modulating autophagy-lysosome function. Furthermore, we conducted pole-climbing behavioral experiments on mice with TFEB overexpression following manganese exposure. Results indicated that TFEB overexpression shortened the time spent at the top and the overall time for mice to climb down compared to the control group. TFEB alleviated the impact of manganese exposure on mouse motor function.

4. Discussion

The central nervous system is a crucial target organ for manganese exposure, considered an important environmental factor in neurodegenerative diseases (Fernandes et al., 2019; Soto-Verdugo and Ortega, 2021). Recent research has revealed the critical role of abnormal protein accumulation in the process of manganese-induced neurological damage (Nyarko-Danquah et al., 2020), particularly the severe impact of excessive accumulation of alpha-synuclein (Ma et al., 2023) and Tau protein (Liu et al., 2022) on neuronal survival.

The nigrostriatal pathway is intimately connected to the coordination of the motor system. Dopaminergic neurons produce the dopamine neurotransmitter, which regulates the motor function of the limbs. The substantia nigra is divided into two parts: the dense part and the reticular part. The dense part primarily consists of the cell bodies of dopaminergic neurons, while the reticular part comprises the axons and dendrites of these neurons. Research has indicated that exposure to manganese can lead to damage in dopaminergic neurons. Consequently, to establish a mouse model for manganese exposure, we administered manganese chloride into the dense part of the substantia nigra.

Tau protein is a microtubule-associated protein and a member of the microtubule protein family (Ukmar-Godec et al., 2020). It is primarily found in neurons and plays a crucial role as an essential protein for maintaining the stability of microtubules within axons (Brunello et al., 2020; Liang et al., 2022). Tau hyperphosphorylation leads to microtubule instability and axonal transport dysfunction (Hu et al., 2023). Hyperphosphorylated Tau protein can self-aggregate into insoluble fibrillary structures, leading to the formation of neurofibrillary tangles, a characteristic pathological feature of Alzheimer's disease (Hamano et al., 2021). Our research demonstrates that manganese exposure significantly elevates Tau protein phosphorylation levels in dopaminergic neurons of the substantia nigra, suggesting that Tau hyperphosphorylation may constitute a critical mechanism underlying manganese-induced neurological damage.

Alpha-synuclein is a soluble protein primarily expressed in presynaptic terminals of neurons. Its normal function remains unclear, but it is closely related to the pathogenesis of Parkinson's disease (Du et al., 2020; Henderson et al., 2019). Alpha-synuclein aggregates into insoluble fibrils and forms Lewy bodies, a hallmark of Parkinson's disease (Mehra et al., 2019). Our results show that manganese exposure significantly increases alpha-synuclein expression levels in dopaminergic neurons of the substantia nigra. Manganese-induced alpha-synuclein aggregation may play a crucial role in neuronal damage.

Autophagy is a vital cellular process that maintains intracellular homeostasis by removing damaged organelles and proteins (D'Arcy, 2019). Dysregulated autophagy contributes to the accumulation of pathological proteins in neurodegenerative diseases (Lou et al., 2020; Rusmini et al., 2019). In our study, manganese exposure increased the number of autophagosomes in dopaminergic neurons, indicating enhanced autophagy formation. However, autophagic flux was disrupted, and autophagosomes remained undegraded. This suggests that autophagy-lysosome dysfunction may be a key factor in manganese-induced neuronal damage.

TFEB is a master regulator of lysosomal biogenesis and function (Li et al., 2022). It controls the expression of genes involved in lysosomal biogenesis, autophagy, and lysosomal acidification (Wang et al., 2020; Yang et al., 2022; Zhang et al., 2022). In our study, manganese exposure suppressed TFEB expression in dopaminergic neurons, resulting in impaired lysosomal function. Notably, overexpression of TFEB mitigated manganese-induced autophagy-lysosome dysfunction, decreased abnormal protein accumulation, and improved motor function in mice.

In conclusion, our study provides novel insights into the mechanisms of manganese neurotoxicity, highlighting the crucial role of autophagy-lysosome dysfunction in the accumulation of pathological proteins. TFEB-mediated restoration of autophagy-lysosome function may represent a promising therapeutic strategy for manganese-induced neurotoxicity and related neurodegenerative diseases. Additionally, TFEB holds potential as an early molecular biomarker for manganese exposure, facilitating early protection and clinical management of manganese-exposed populations. Further research is needed to explore the translational potential of these findings for human health and safety.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

This work was supported by National Natural Science Foundation of China (No. 82273592, No. 82073500); Shaanxi Outstanding Youth Fund Project (2023-JC-JQ-65) and Air Force Medical University incubation pre-research program (2022-fhjsyxrc04).

References

Ballabio, A., Bonifacino, J.S., 2020. Lysosomes as dynamic regulators of cell and organismal homeostasis. Nat. Rev. Mol. Cell Biol. 21, 101–118. https://doi.org/10.1038/s41580-019-0185-4.

Brunello, C.A., Merezhko, M., Uronen, R.L., Huttunen, H.J., 2020. Mechanisms of secretion and spreading of pathological tau protein. Cell. Mol. Life Sci. 77, 1721–1744. https://doi.org/10.1007/s00018-019-03349-1.

Cao, W., Li, J., Yang, K., Cao, D., 2021. An overview of autophagy: Mechanism, regulation and research progress. Bull. Cancer 108, 304–322. https://doi.org/10.1016/j.bulcan.2020.11.004.

D'Arcy, M.S., 2019. Cell death: a review of the major forms of apoptosis, necrosis and autophagy. Cell Biol. Int. 43, 582–592. https://doi.org/10.1002/cbin.11137.

Dlamini, W.W., Nelson, G., Nielsen, S.S., Racette, B.A., 2020. Manganese exposure, parkinsonian signs, and quality of life in South African mine workers. Am. J. Ind. Med. 63, 36–43. https://doi.org/10.1002/ajim.23060.

Du, X.Y., Xie, X.X., Liu, R.T., 2020. The role of α-synuclein oligomers in Parkinson's disease. Int. J. Mol. Sci. 21 https://doi.org/10.3390/ijms21228645.

Erikson, K.M., Aschner, M., 2019. Manganese: its role in disease and health. Metal Ions Life Sci. 19 https://doi.org/10.1515/9783110527872-016.

Fernandes, J., Chandler, J.D., Liu, K.H., Uppal, K., Hao, L., Hu, X., Go, Y.M., Jones, D.P., 2019. Metabolomic responses to manganese dose in SH-SY5Y human neuroblastoma cells. Toxicol. Sci. 169, 84–94. https://doi.org/10.1093/toxsci/kfz028.

Franco-Juárez, B., Coronel-Cruz, C., Hernández-Ochoa, B., Gómez-Manzo, S., Cárdenas-Rodríguez, N., Arreguin-Espinosa, R., Bandala, C., Canseco-Ávila, L.M., Ortega-Cuellar, D.T.F.E.B., 2022. Beyond Its Role as an Autophagy and Lysosomes Regulator. Cells-Basel 11. https://doi.org/10.3390/cells11193153.

Geibl, Fanni F., Henrich, Martin T., Xie, Zhong, Zampese, Enrico, Tkatch, Tatiana, Wokosin, David L., Nasiri, Elena, Grotmann, Constantin A., Dawson, Valina L., Dawson, Ted M., Chandel, Navdeep S., Oertel, Wolfgang H., James Surmeier, D., 2023. α-Synuclein pathology disrupts mitochondrial function in dopaminergic and cholinergic neurons at risk in Parkinson's disease. Bio Rxiv, 571045. https://doi.org/10.1101/2023.12.11.571045.

Hamano, T., Enomoto, S., Shirafuji, N., Ikawa, M., Yamamura, O., Yen, S.H., Nakamoto, Y., 2021. Autophagy and tau protein. Int. J. Mol. Sci. 22 https://doi.org/10.3390/ijms22147475.

Henderson, M.X., Trojanowski, J.Q., Lee, V.M., 2019. α-Synuclein pathology in Parkinson's disease and related α-synucleinopathies. Neurosci. Lett. 709, 134316 https://doi.org/10.1016/j.neulet.2019.134316.

Hu, J., Sha, W., Yuan, S., Wu, J., Aggregation, H.Y., 2023. Transmission, and toxicity of the microtubule-associated protein tau: a complex comprehension. Int. J. Mol. Sci. 24 https://doi.org/10.3390/ijms241915023.

Ijomone, O.M., Aluko, O.M., Okoh, C., Martins, A.J., Aschner, M., 2019. Role for calcium signaling in manganese neurotoxicity. J. Trace Elem. Med Biol. 56, 146–155. https://doi.org/10.1016/j.jtemb.2019.08.006.

Lee, E.Y., Flynn, M.R., Du, G., Lewis, M.M., Kong, L., Yanosky, J.D., Mailman, R.B., Huang, X., 2019. Higher hippocampal mean diffusivity values in asymptomatic welders. Toxicol. Sci. 168, 486–496. https://doi.org/10.1093/toxsci/kfz011.

Levine, B., Kroemer, G., 2019. Biological functions of autophagy genes: a disease perspective. Cell 176, 11–42. https://doi.org/10.1016/j.cell.2018.09.048.

Li, T., Yin, L., Kang, X., Xue, W., Wang, N., Zhang, J., Yuan, P., Lin, L., Li, Y., 2022. TFEB acetylation promotes lysosome biogenesis and ameliorates Alzheimer's disease-relevant phenotypes in mice. J. Biol. Chem. 298, 102649 https://doi.org/10.1016/j.jbc.2022.102649.

Liang, S.Y., Wang, Z.T., Tan, L., Yu, J.T., 2022. Tau toxicity in neurodegeneration. Mol Neurobiol 59, 3617–3634. https://doi.org/10.1007/s12035-022-02809-3.
Liu, J., Zhang, X., Wang, H., 2022. The cGAS-STING-mediated NLRP3 inflammasome is involved in the neurotoxicity induced by manganese exposure. Biomed. Pharmacother. 154, 113680 https://doi.org/10.1016/j.biopha.2022.113680.
Lou, G., Palikaras, K., Lautrup, S., Scheibye-Knudsen, M., Tavernarakis, N., Fang, E.F., 2020. Mitophagy and neuroprotection. Trends Mol. Med. 26, 8–20. https://doi.org/10.1016/j.molmed.2019.07.002.
Ma, Z., Wang, C., Liu, C., Yan, D.Y., Tan, X., Liu, K., Jing, M.J., Deng, Y., Liu, W., Xu, B., 2020. Manganese induces autophagy dysregulation: The role of S-nitrosylation in regulating autophagy related proteins in vivo and in vitro. Sci. Total Environ. 698, 134294 https://doi.org/10.1016/j.scitotenv.2019.134294.
Ma, Z., Liu, K., Zhang, R.F., Xie, Z.X., Liu, W., Deng, Y., Li, X., Xu, B., 2023. Manganese-induced α-synuclein overexpression promotes the accumulation of dysfunctional synaptic vesicles and hippocampal synaptotoxicity by suppressing Rab26-dependent autophagy in presynaptic neurons. Sci. Total Environ. 858, 159753 https://doi.org/10.1016/j.scitotenv.2022.159753.
Martins, A.J., Morcillo, P., Ijomone, O.M., Venkataramani, V., Harrison, F.E., Lee, E., Bowman, A.B., Aschner, M., 2019. New insights on the role of manganese in Alzheimer's disease and Parkinson's disease. Int. J. Environ. Res. Public Health 16. https://doi.org/10.3390/ijerph16193546.
Mehra, S., Sahay, S., Maji, S.K., 2019. α-Synuclein misfolding and aggregation: Implications in Parkinson's disease pathogenesis. Biochim. Biophys. Acta Proteins Proteom. 1867, 890–908. https://doi.org/10.1016/j.bbapap.2019.03.001.
Mezzaroba, L., Alfieri, D.F., Colado Simão, A.N., Vissoci Reiche, E.M., 2019. The role of zinc, copper, manganese and iron in neurodegenerative diseases. Neurotoxicology 74, 230–241. https://doi.org/10.1016/j.neuro.2019.07.007.
Nyarko-Danquah, I., Pajarillo, E., Digman, A., Soliman, K., Aschner, M., Lee, E., 2020. Manganese accumulation in the brain via various transporters and its neurotoxicity mechanisms. Molecules 25. https://doi.org/10.3390/molecules25245880.
Pajarillo, E., Nyarko-Danquah, I., Digman, A., Multani, H.K., Kim, S., Gaspard, P., Aschner, M., Lee, E., 2022. Mechanisms of manganese-induced neurotoxicity and the pursuit of neurotherapeutic strategies. Front. Pharmacol. 13, 1011947. https://doi.org/10.3389/fphar.2022.1011947.
Park, H.S., Song, J.W., Park, J.H., Lim, B.K., Moon, O.S., Son, H.Y., Lee, J.H., Gao, B., Won, Y.S., Kwon, H.J., 2021. TXNIP/VDUP1 attenuates steatohepatitis via autophagy and fatty acid oxidation. Autophagy 17, 2549–2564. https://doi.org/10.1080/15548627.2020.1834711.
Rusmini, P., Cortese, K., Crippa, V., Cristofani, R., Cicardi, M.E., Ferrari, V., Vezzoli, G., Tedesco, B., Meroni, M., Messi, E., et al., 2019. Trehalose induces autophagy via lysosomal-mediated TFEB activation in models of motoneuron degeneration. Autophagy 15, 631–651. https://doi.org/10.1080/15548627.2018.1535292.
Soto-Verdugo, J., Ortega, A., 2021. Critical involvement of glial cells in manganese neurotoxicity. Biomed Res. Int. 2021, 1596185. https://doi.org/10.1155/2021/1596185.
Tinkov, A.A., Paoliello, M., Mazilina, A.N., Skalny, A.V., Martins, A.C., Voskresenskaya, O.N., Aaseth, J., Santamaria, A., Notova, S.V., Tsatsakis, A., et al., 2021. Molecular targets of manganese-induced neurotoxicity: a five-year update. Int. J. Mol. Sci. 22 https://doi.org/10.3390/ijms22094646.
Ukmar-Godec, T., Wegmann, S., Zweckstetter, M., 2020. Biomolecular condensation of the microtubule-associated protein tau. Semin. Cell Dev. Biol. 99, 202–214. https://doi.org/10.1016/j.semcdb.2019.06.007.
Vargas, J., Hamasaki, M., Kawabata, T., Youle, R.J., Yoshimori, T., 2023. The mechanisms and roles of selective autophagy in mammals. Nat. Rev. Mol. Cell Biol. 24, 167–185. https://doi.org/10.1038/s41580-022-00542-2.
Wang, Y., Huang, Y., Liu, J., Zhang, J., Xu, M., You, Z., Peng, C., Gong, Z., Liu, W., 2020. Acetyltransferase GCN5 regulates autophagy and lysosome biogenesis by targeting TFEB. EMBO Rep. 21, e48335.
Yan, S., 2022. Role of TFEB in autophagy and the pathogenesis of liver diseases. Biomolecules 12. https://doi.org/10.3390/biom12050672.
Yan, D.Y., Xu, B., 2020. The role of autophagy in manganese-induced neurotoxicity. Front. Neurosci. 14, 574750 https://doi.org/10.3389/fnins.2020.574750.
Yan, D.Y., Liu, C., Tan, X., Ma, Z., Wang, C., Deng, Y., Liu, W., Xu, Z.F., Xu, B., 2019. Mn-induced neurocytes injury and autophagy dysfunction in alpha-synuclein wild-type and knock-out mice: highlighting the role of alpha-synuclein. Neurotox. Res. 36, 66–80. https://doi.org/10.1007/s12640-019-00016-y.
Yang, C., Su, C., Iyaswamy, A., Krishnamoorthi, S.K., Zhu, Z., Yang, S., Tong, B.C., Liu, J., Sreenivasmurthy, S.G., Guan, X., et al., 2022. Celastrol enhances transcription factor EB (TFEB)-mediated autophagy and mitigates Tau pathology: Implications for Alzheimer's disease therapy. Acta Pharm. Sin. B 12, 1707–1722. https://doi.org/10.1016/j.apsb.2022.01.017.
Zhang, W., Xu, C., Sun, J., Shen, H.M., Wang, J., Yang, C., 2022. Impairment of the autophagy-lysosomal pathway in Alzheimer's diseases: Pathogenic mechanisms and therapeutic potential. Acta Pharm. Sin. B 12, 1019–1040. https://doi.org/10.1016/j.apsb.2022.01.008.
Zhang, Z., Yan, J., Bowman, A.B., Bryan, M.R., Singh, R., Aschner, M., 2020. Dysregulation of TFEB contributes to manganese-induced autophagic failure and mitochondrial dysfunction in astrocytes. Autophagy 16, 1506–1523. https://doi.org/10.1080/15548627.2019.1688488.
Zhang, Z., Yue, P., Lu, T., Wang, Y., Wei, Y., Wei, X., 2021. Role of lysosomes in physiological activities, diseases, and therapy. J. Hematol. Oncol. 14, 79. https://doi.org/10.1186/s13045-021-01087-1.