Int. J. Morphol.,
41(3):811-818, 2023.

HDAC2 Inhibits Hippocampal Neurogenesis and Impairs the Cognitive Function in Prenatally Stressed Adult Offspring

HDAC2 Inhibe la Neurogénesis del Hipocampo y Afecta la Función Cognitiva en la Descendencia Adulta Estresada Prenatalmente

Libin Liao[1, 2]; BingRu Chai[2]; Tian Zhao[4]; Wentao Liu[2]; Xinyi Zhang[2]; Xiaoxu Xu[2]; Xiaohan Tian[2]; Mengjiao Lv[3]; Xueping Yao[1] & Shengbin Bai[2]

LIAO, L.; CHAI, B. R.; ZHAO, T.; LIU, W.; ZHANG, X.; XU, X.; TIAN, X.; LV, M.; YAO, X. & BAI, S. HDAC2 inhibits hippocampal neurogenesis and impairs the cognitive function in prenatally stressed adult offspring. *Int. J. Morphol., 41(3)*:811-818, 2023.

SUMMARY: The objective of this study was to investigate the mechanism of prenatal stress on the cognitive function of offspring, and clarify the change of histone deacetylase 2 (HDAC2) expression in hippocampal neurons of offspring. 16 pregnant SD rats were randomly divided into control group and stress group, with eight rats in each group. The stress group received restrained stress from 15 to 21 days of pregnancy, while the control group did not receive any treatment. Anxiety-like behavior and spatial memory,learning and memory ability were detected in open field, elevated plus maze, novel object recognition test, and Barnes maze. Nissl staining was used to detect the function of hippocampal neurons. Western blot was used to detect the expression of HDAC2 protein in hippocampal neurons of adult offspring. Immunofluorescence staining was used to detect the expression of HDAC2 protein and hippocampal neurogenesis. The learning and memory ability of adult offspring was decreased.The prenatal stress damaged the function of hippocampal neurons , the expression of HDAC2 was down-regulated, and the number of neurons was reduced. Maternal prenatal stress can down-regulate the expression of HDAC2 in the hippocampus of offspring, inhibits hippocampal neurogenesis and impairs the cognitive function.

KEY WORDS: HDAC2; Stress; Cognitive impairment; Epigenetics.

INTRODUCTION

Pregnancy is the key period of offspring shaping. Adverse intrauterine environment, such as mother's stressful experience during or even before pregnancy, prenatal depression and anxiety, previous experience of abuse as a child, or exposure to stressful environment during pregnancy, such as loss of relatives or natural disasters. These are associated with various cognitive and motor disorders, personality changes, and increased risk of mental illness in offspring in adulthood. Environmental exposure can affect the development and interaction of cells and tissues in a sensitive and critical period, thus having a lasting impact on human health (Wong & Herbert, 2006; Monk *et al*., 2019).

Accumulating evidence from animal and human studies show that prenatal stress can reprogram the brain development of offspring and then lead to neurocognitive dysfunction after birth. Neuroimaging studies have shown that prenatal stress is related to changes in brain structure and development trajectory. This effect will be accompanied by the delivery and growth of the fetus (Koenig *et al*., 2002; Pham *et al*., 2003; McEwen & Gianaros, 2011; Bock *et al*., 2015; Egeland *et al*., 2015; Kim *et al*., 2015; Grant *et al*., 2016; O'Donnell & Meaney, 2017; Osborne *et al*., 2018).

The over-activation of the hypothalamus-pituitary adrenaline axis (HPA axis) in the maternal generation leads to excessive glucocorticoids, which is generally recognized as the main mechanism of stress damage in prenatally stressed adult offspring. Excessive glucocorticoid can cross the placental barrier and reprogram the fetal brain, resulting

[1] Key Laboratory of Special Environment and Health Research in Xinjiang, Urumqi, P. R. China.
[2] Department of histology and embryology, School of basic medicine, Xinjiang Medical University, Urumqi, P. R. China.
[3] Functional Center, School of basic medicine, Xinjiang Medical University, Urumqi, P. R. China.
[4] Clinical departments, School of medicine, 2018-7, Xinjiang Medical University, Xinjiang, Urumqi, P. R. China.
FUNDING. Supported by the Key Laboratory of Special Environment and Health Research in Xinjiang (No. SKL-SEHR-2021-08).

Received: 2023-03-21 Accepted: 2023-04-17

in adult cognitive dysfunction. However, little is known about how glucocorticoids affect reprogramming in the fetal brain. Studies have shown that epigenetic regulation is an important mechanism affecting the individual brain and environmental factors. Histone deacetylases (HDACs) are important epigenetic modifying enzymes related to learning, memory, and synaptic plasticity genes. HDAC2 is considered to be the most important regulatory molecule. In this study, Nissl staining was used to detect the function of hippocampal neurons in adult offspring. Western blot and immunohistochemistry were used to detect the expression of HDAC2 in hippocampal neurons in postnatal 0 day (P0) and adult offspring. Revealing how HDAC2 affects the function of neurons, providing new theoretical support and new drug treatment targets for the mechanism of cognitive impairment in prenatally stressed adult offspring .

MATERIAL AND METHOD

Animals. Adult female Sprague-Dawley rats (250–300 g) were used in this study. They were housed in an animal care facility within the Department of Laboratory Animals in Central South University, Hunan, P.R. China, under stable temperature (22 ± 1°C) and lighting conditions (12-h light/12-h dark cycle). Food and water were provided, along with constant care and clean conditions. All animal experiments were conducted in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23), revised in 1996, and were approved by the Animal Ethics Committee of the Xinjiang Medical University (Urumqi, China). All efforts were taken to minimize the number, suffering, and discomfort of all laboratory animals used in this study.

Prenatal stress procedure. Pregnant females were housed individually and were randomly assigned to a stressed (n =8) or control (n = 8) group. The prenatal stress protocol was adapted from previous studies and was performed at the last week of pregnancy. Pregnant dams were placed into transparent plastic restrainers (8.6 cm in diameter ¥ 21.6 cm in length) at 09:00 h, 13:00 h, and 17:00 h for 45 min daily.Control dams were left undisturbed in their home cages. After birth, the pups were raised with their mothers. The offspring were weaned on postnatal day 21 and group-housed with littermates of the same sex.

Behavioral Test

Open Field Test. The open field is a novel, stressful environment in which the animals are placed in an open arena; this test was performed as previously described (Hoban *et al*., 2016). An open-field chamber (width: 100 cm, length: 100 cm, height: 40 cm), which was separated into 25 squares, was used. Thirty minutes before the behavioral test, the animals were habituated to the room. Rats were placed in the center and allowed to explore the apparatus for 5 min. After the 5-minute test, rats were returned to their home cages, and the open field was cleaned with 75 % ethyl alcohol and permitted to dry between tests. The behavioral score included the following: the number of line crossings, which was defined as the frequency with which the rat crossed one of the grid lines with all four paws, and the center square duration, which was defined as the duration of time the rat spent in the central square.

Novel Object Recognition Test. The novel object recognition test is used to evaluate the ability of an animal to recognize a novel object in an environment (Gur, *et al*., 2016). The test consisted of two phases: the familiarization phase and test phase. During the familiarization phase, two identical objects were placed in the arena, and the animal was placed in the arena facing away from the objects. After exposure to the sample object for a defined period (10 min), the animal was removed and returned to its home cage. Twenty-four hours after the familiarization phase, one of the objects was exchanged with a new one. The animal was placed back in the arena with the novel object and the other familiar object for 10 min. The testing arena and objects were cleaned with 75 % ethanol. Videos were scored by trained observers, and the measures of direct contact with an object (including any contact using the mouth, nose or paw) were manually scored. Novel object preference was assessed by determining the time spent investigating the original object and the time spent investigating the novel object in relation to the total time spent investigating both objects.

Elevated Plus-Maze. The elevated plus-maze is a common paradigm used to investigate anxiety-like behaviors in rodents; this maze was implemented as described in a previous study (O'Mahony *et al*., 2015). The animals were habituated to the testing room for 30 min prior to the test.The maze was elevated 750 mm from the floor, comprising two open and two closed arms (100×500×400 mm walls, W×L×H). All arms of the maze were cleaned with 75 % ethanol before the introduction of the animal. Each animal was placed on the center platform facing the open arm and allowed to explore the maze for 5 min. The time spent in each arm and the number of entries into the open and closed arms were manually scored.

Barnes Maze. The Barnes maze was used to test the spatial learning and memory abilities of the subjects. The maze used in the present study was a white, circular disk (122 cm in diameter) with 18 holes (every 20°, close to the edge of the disk, 9.5 cm in diameter) and a high stand (140 cm height)

supporting the disk. The first trial was the habituation phase. Each rat was placed in a cylindrical black start chamber in the middle of the maze. After 15 s had elapsed, the chamber was lifted. Then, the rat was exposed to a bright light and gently guided to the escape box. The rat was allowed 3 min to search for the escape box following stimulation with the same light. If the rat failed to locate the escape box, it was gently guided to the box. Once the rat was inside the box, the light was turned off, and the rat was permitted to stay in the escape box for 2 min. The hole was covered with a black sheet. The spatial location of the target box and the corresponding hole were relatively fixed over the 4-day test (3 trials/day), as were the spatial cues in the room. The rat was then returned to its home cage for a 15-min interval before the next trial. Between each trial, the surface of the disk was cleaned with 75 % ethanol to remove the odor cues. The escape latency to reach the target hole and the escape errors were recorded and compared.

Nissl staining. The frozen sections were dried in the air, dehydrated in 75 % alcohol, dried, and placed in Nissl staining solution (n21479; Life technologies, CA, USA). Rinse the glass slide gently with tap water, transparent with xylene, and sealed with neutral gum,observe under the microscope.

Immunohistochemistry. The hippocampal tissue of rats was fixed with 4 % paraformaldehyde for 24 hours, then dehydrated with 15 % sucrose for 24 hours and 30 % sucrose for 48 hours. The tissue was embedded with o.c.t. the slices were sectioned with a 20 mm thick frozen section machinemm. PBS the slices were rinsed three times and then placed in 3 % H2O2 solution for 10 minutes; PBS was rinsed three times, and 5 % calf serum (BSA, Sigma, Mo, USA) was sealed at room temperature for 1 h; Rabbit anti HDAC2 (1:200; Protentech group, Wuhan) 4 °C overnight; The next day, the rabbits were rinsed with PBS and incubated with biotinylated Goat anti-rabbit IgG at room temperature for 1 h (1:200; Vector Laboratories, USA)?The cells were rinsed with PBS and incubated with ABC (1:1:400? vector laboratories, USA) solution for 2 h at room temperature; PBS was rinsed for 3 times, DAB was used for color development, and then pasted, dehydrated, transparent and sealed, and the results were observed under the microscope.

Immunofluorescence staining. The specific method is referred to (Zaba *et al*., 2009). After slicing, the slices were washed with PBS 3 times, 5 minutes each time.BSA (5 %) and 0.3 % Triton were sealed at room temperature for 1 h.Primary antibody: Rabbit anti HDAC2 (1:200;Protentech group, Wuhan), rat anti DCX (Abcam, 1:1000), mixed with 0.3 % Triton and 5 % BSA, incubated overnight at 4 ?.The next day, take out and rewarm for 30min, and wash with PBS 3 times, 5min each time. Second antibody incubation: Cy3 labeled donkey anti-rabbit IgG (Jackson immune research, 1:400) and Alexa fluor 488 labeled donkey anti-rat IgG (Jackson immune research, 1:400).3 % Triton, 5 % BSA, incubated at room temperature for two hours in the dark. PBS washed 3 times, 5 min each time; The films were sealed with DAPI and photographed with Nikon's confocal microscope.

Western blotting. The hippocampal tissue of adult offspring was added with protein lysate np40, and an electric homogenizer lysed the tissue at 15000r / min for 10min. After centrifugation, the supernatant was obtained, and the protein was quantified by BCA Kit (Kangwei century Biotechnology Co., Ltd., Beijing) (4mg/ml). The protein of each sample was separated by SDS-PAGE gel and then transferred to PVDF membrane (Bio-Rad, CA, USA). The test was rinsed three times for 15 minutes, 5 % skim milk was sealed at room temperature for 1 hour, and the first antibody was incubated (Rabbit anti HDAC2, 1:800; Protentech) 4 °C overnight. The next day, the second antibody was incubated at room temperature for 1 h, and Odyssey was washed® FC imaging system (Li cor Biosciences, USA) was used to observe the bands. Image J was used to analyze the optical density of the bars quantitatively.

Statistical analysis. SPSS 19.0 statistical software was used for analysis. The data were expressed as X±S. Repeated measures ANOVA was used for Barnes maze data, and an unpaired t-test was used for comparison among other data groups. $P<0.05$ was considered statistically significant.

RESULTS

Prenatal stress impairs cognitive function in adult offspring. The open-field showed that the movement distance of the offspring between the control group and stress group was almost the same (Fig. 1A), and the residence time in the central area of the stress group was significantly reduced compared with the control group (Fig. 1B), The novel object recognition showed that there was no significant difference in the contact time between the control group and the stress group (Fig. 1C), and the recognition rate of the stress group was significantly lower than that of the control group (Fig. 1D); The elevated plus maze test showed that compared with the control group, the times and entries in the open arm were both decreased in the stress group (Figs. 1E,F), In the Barnes maze test, data were analyzed by repeated measures ANOVA. The errors of prenatally stressed offspring were significantly more than that of control offspring, whereas there was no difference between prenatally stressed offspring and control offspring.

Prenatal stress damages hippocampal neurons of adult offspring. The results of Nissl staining showed that the

hippocampal neurons in the control group had deep staining, a large number of Nissl bodies, dense arrangement, unmistakable outline, and clear structure (Figs. 2A-C), while the neurons in the stress group had light staining, relatively vague external and internal system, and a small number of Nissl bodies (Figs. 2D-F).

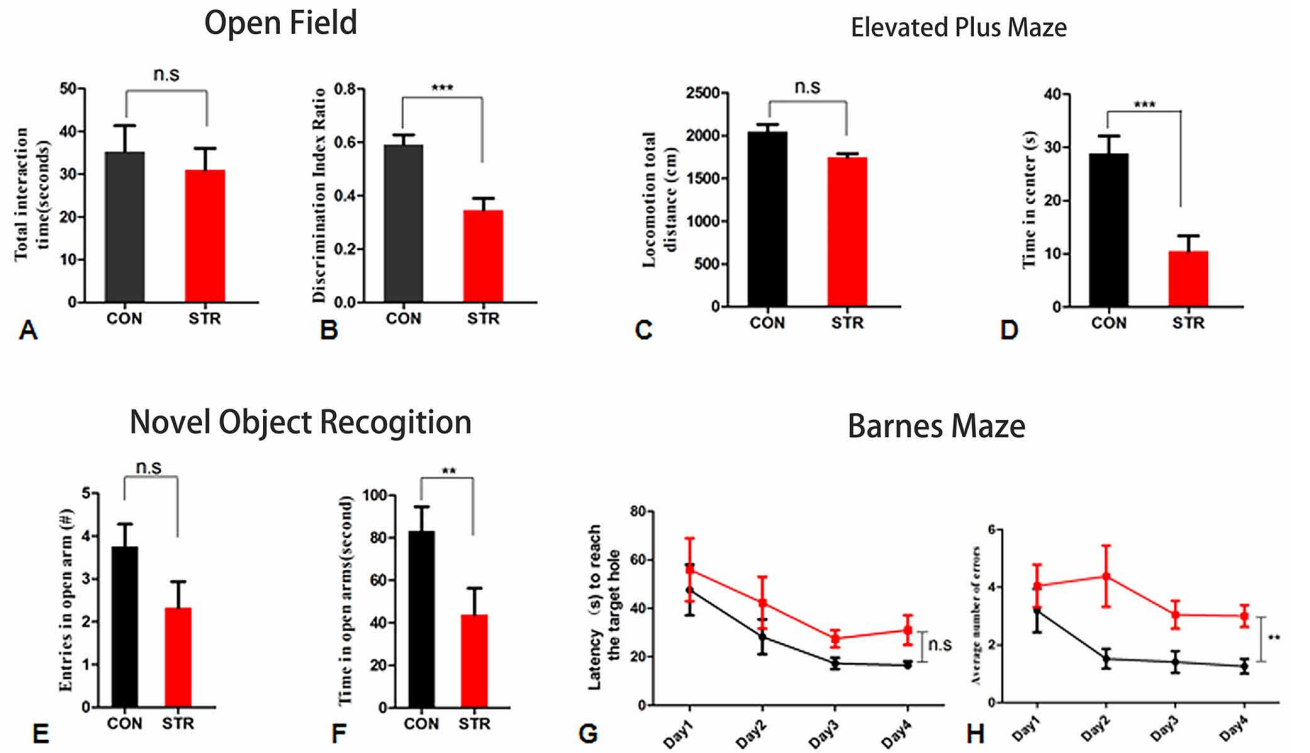

Fig. 1. Behavioral test of the effect of prenatal stress on cognitive function of adult offspring. A, Total distance of open field movement; B, Open field central retention area time; C, Contact time of new object recognition; D, New object recognition rate; E, The number of times the elevated maze entered the open arm; F, The total time for the elevated maze to enter the open arm; G, Latency of Barnes maze; H, The number of mistakes in Barnes maze; CON, control group; STR, prenatally stressed offspring.. **, P < 0.05; ***, P<0.01

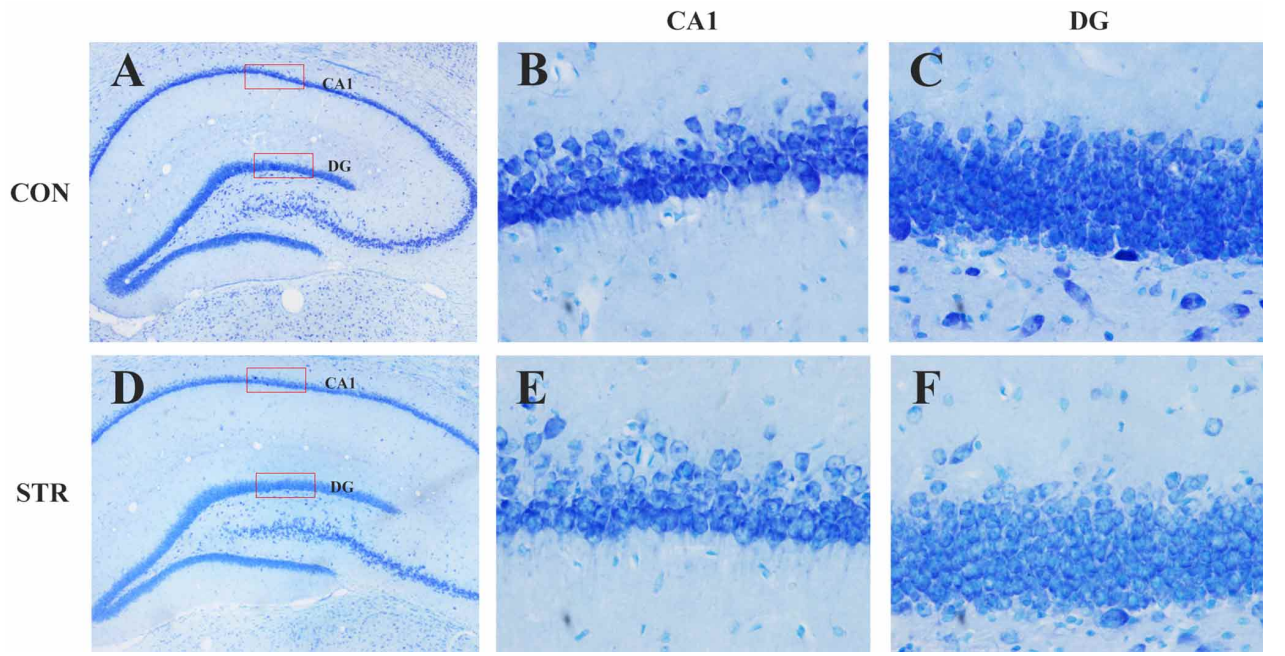

Fig. 2. Nissl sating in the hippocampus of adult offspring. A B C, control group;D E F, stress group.A D, magnification 40 times;B C E F, magnification 400 times. CON, control group; STR, prenatally stressed offspring.

Prenatal stress down-regulates the expression of HDAC2 in hippocampal neurons of adult offspring. Immunohistochemistry showed that HDAC2 was widely expressed in hippocampal neurons. In the control group, HDAC2 was expressed in both the cell body and nucleus of neurons, and the expression of HDAC2 was relatively uniform in all neurons (Figs. 3A-C); In the stress group, HDAC2 was also expressed in the cell body and nucleus of neurons, and the whole neurons were uniformly stained (Figs. 3D-F). Immunofluorescence results showed that the expression of HDAC2 in hippocampal neurons of adult offspring was down-regulated in CA1 and DG regions during pregnancy (Fig. 4). Western blotting results were consistent with immunofluorescence results (Fig. 5).

HDAC2 inhibits hippocampal neuronal neogenesis in prenatally stressed adult offspring. Immunofluorescence detection showed that DCX positive cells were found in the DG area of the hippocampus in both the control group and the stress group. DCX (doublecortin) was mainly expressed in neurons' cell bodies and processes in the subgranular layer, and the methods extended from the subgranular layer to the molecular layer. There were no branches in the granular cell layer, and there were many small branches after entering the molecular layer. Both the control group and the stress group had expression in the cell bodies of the hippocampal neurons in the granular layer, but the branches in the molecular layer were significantly reduced in the stress group (Fig. 6).

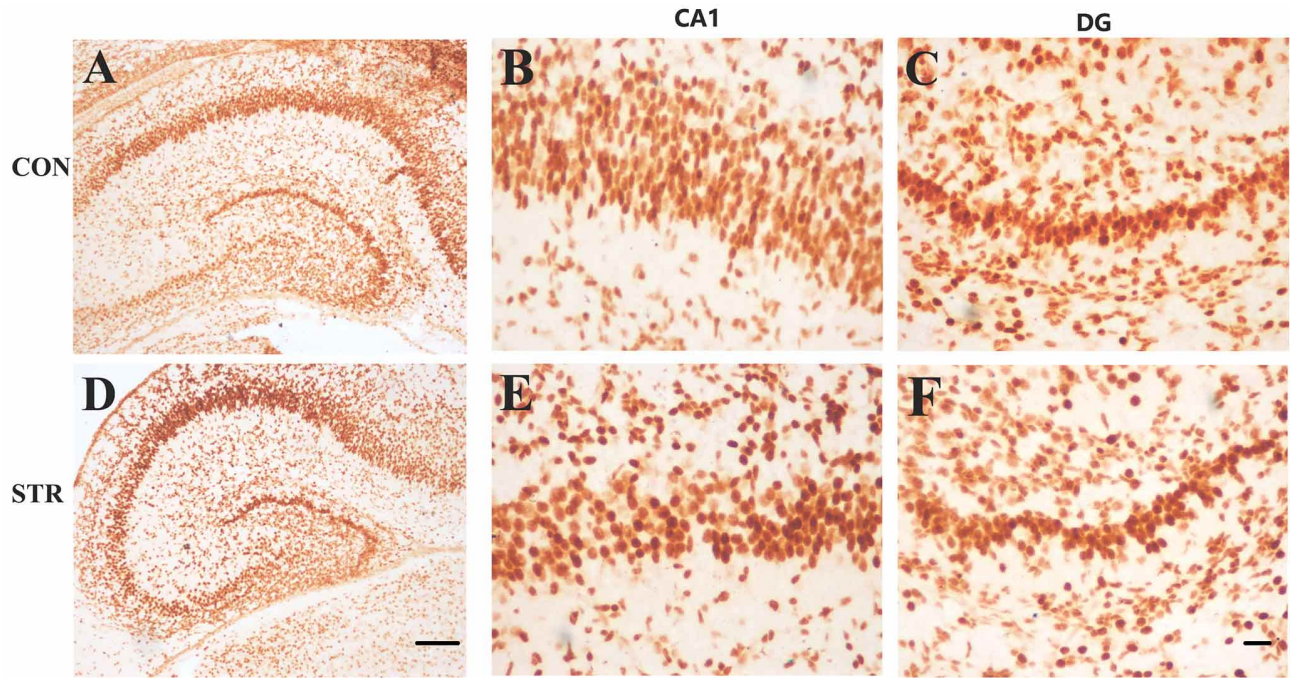

Fig. 3. Results of immunofluorescence staining in hippocampus of postnatal 0 day offspring A - C, control group; D - E, prenatally stressed offspring. Scale: A, D, 100 μm; B C E F, 50 μm.

DISCUSSION

HDAC2 plays an essential role in regulating synaptic plasticity in the adult brain (Penney & Tsai, 2014). Activation of endogenous HDAC2 can inhibit synaptic plasticity and various forms of learning and memory (White & Wood, 2014). Overexpression of HDAC2 can reduce the number of dendritic spines and synapses in hippocampal neurons and damage memory ability (Mychasiuk *et al*., 2012). HDAC2 knockout mice showed enhanced learning and memory, and synaptic plasticity (Hausknecht *et al*., 2013). Therefore, the expression of HDAC2 has a negative correlation with the cognitive, education, and memory functions of the offspring. Our results indicate that the down-regulation of HDAC2 expression in offspring is also accompanied by cognitive dysfunction. This may be caused by the different times and ways of stress during pregnancy. The time and mode of prenatal stress is an essential factor that affects and determines stress results (Ellman *et al*., 2008). However, little is known about how HDAC2 changes affect the function of neurons.

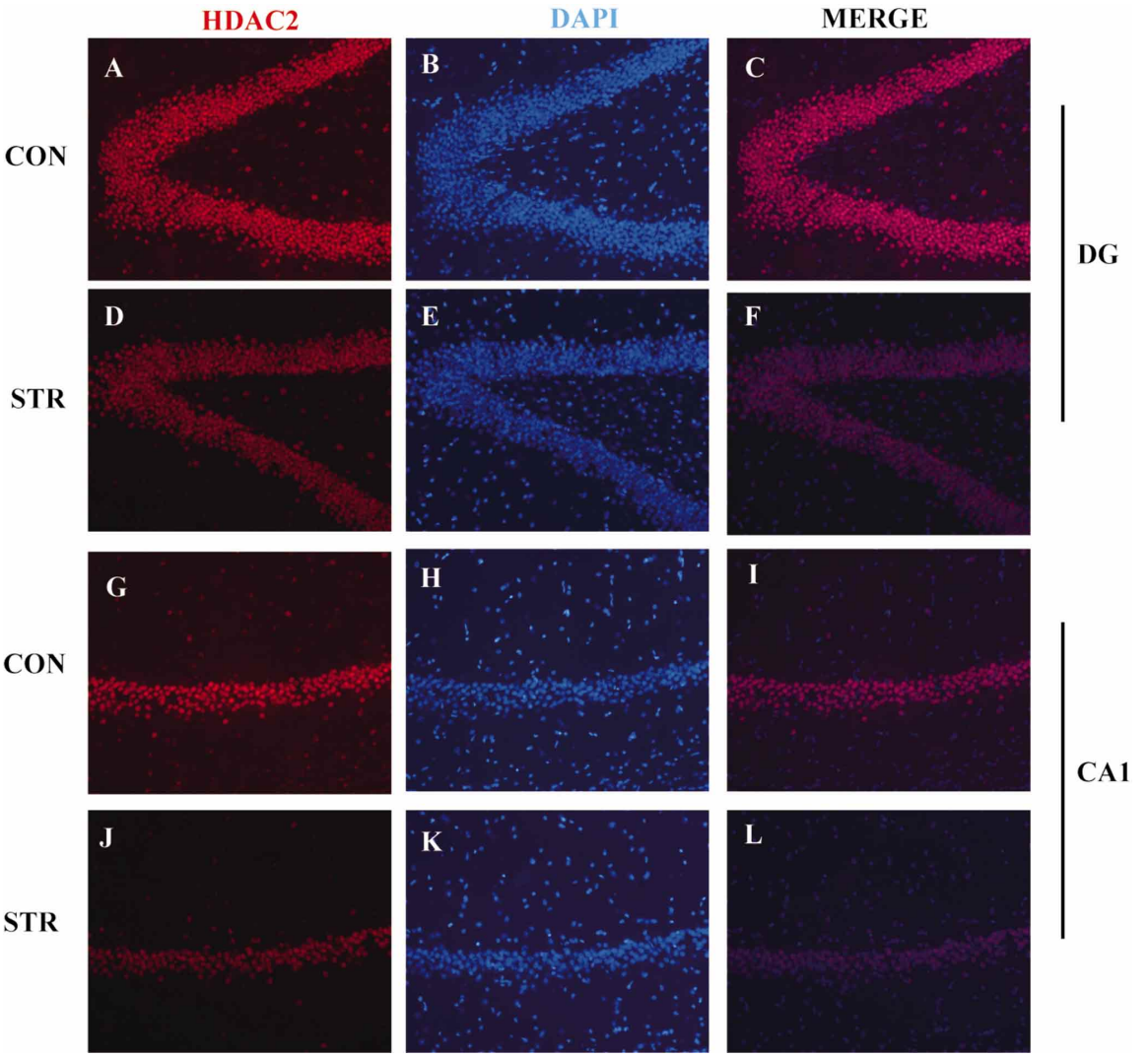

Fig. 4. Fluorescence immunostaining of HDAC2 in adult offspring hippocampus : The typical distributions of HDAC2 (red) and DAPI (blue) in the hippocampal CA1 and DG area. A-F: the DG area of hippocampus ,G-L:the CA1 area of hippocampus , The overlapping of DAPI stained nuclei (blue) and HDAC2 (red) presenting as purple in he merged panel:control group; CON, control group; STR: prenatally stressed offspring.

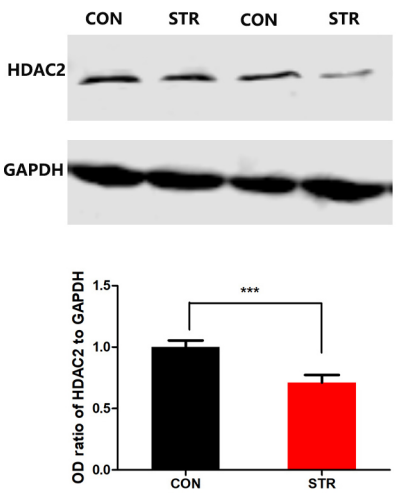

Fig. 5. Western blot was used to detect the expression of HDAC2 in the hippocampus of adult offspring. CON, control group; STR, prenatally stressed offspring,*** P <0.01

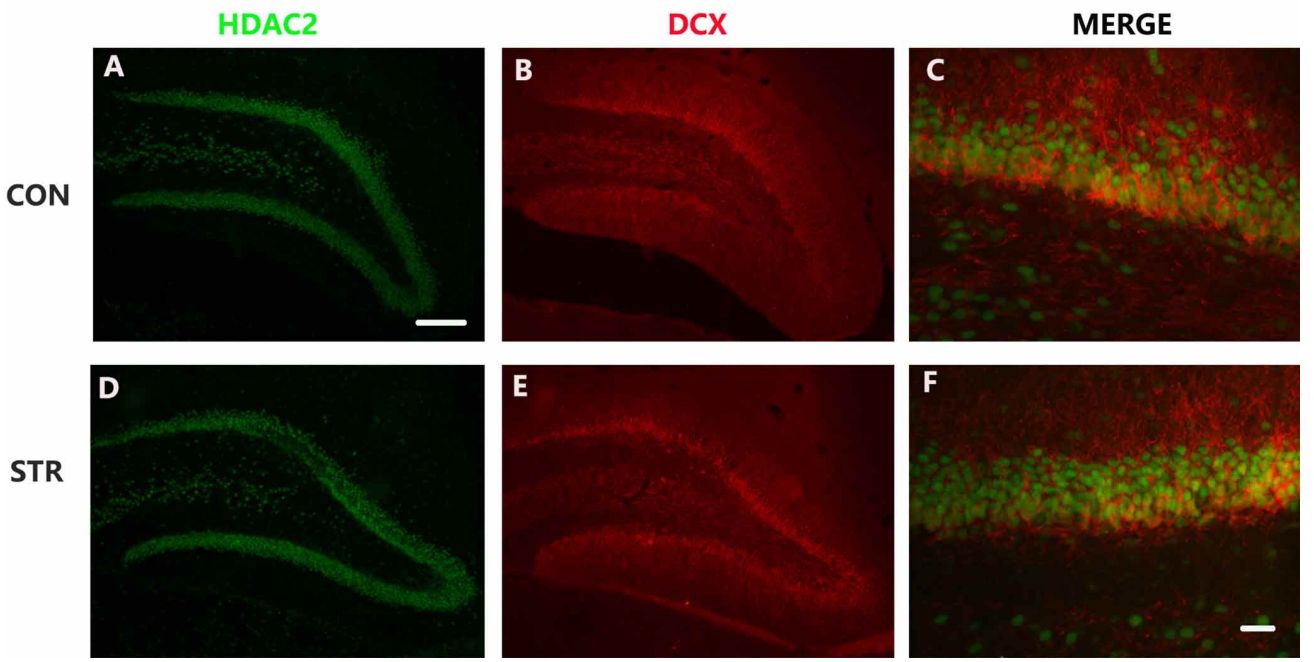

Fig. 6. Immunofluorescence staining of neurons in the hippocampus of adult offspring. The typical distributions of HDAC2 (green) and DCX(red) in the hippocampal.The co-location of HDAC2 (green) and DCX(red) in the neurons of hippocampal CA1 areas in he merged panel. Scale: A, B, D, E: 100 μm; C , F: 50 μm. CON, control group; STR, prenatally stressed offspring.

The number of new neurons can be increased or decreased under different external stimuli, such as physical exercise or environmental enrichment, which can improve the regeneration of neurons in the DG area of the hippocampus. On the other hand, stress, aging, and depression can reduce neuronal regeneration. Some evidence about the relationship between adult neuronal neogenesis and learning and memory come from the counting of newborn neurons. Exposing animals to a rich environment can increase the occurrence of neurons and enhance their performance in spatial memory tests, such as water maze and new object recognition. These results indicate that there is a dependent relationship between learning and memory function of the hippocampus and DG neuron regeneration (Kempermann *et al*., 1997; van Praag *et al*., 1999; Duman, 2004; Dhanushkodi *et al*., 2007).

Adult neurogenesis is a complex process affected by many factors, such as neurotransmitters, metabolites, hormones, etc. Mirescu & Gould (2006) found that adult hippocampal neurons are susceptible to stress and glucocorticoid. Recently, Anacker *et al*. (2018) reported that hippocampal neurogenesis could resist chronic stress injury by inhibiting the activity of granule cells in the ventral dentate gyrus.

In a recent study, targeted deletion of HDAC2 impairs the maturation of newborn neurons in the adult brain (Guan *et al*., 2009) . Our results suggest that prenatal stress down-regulates the expression of HDAC2 in hippocampal neurons of adult offspring, and the number of hippocampal neurons decreased in prenatally stressed adult offspring. In addition, the expression of HDAC2 in the postnatal development of hippocampal neurons of rats is different in time and space, and there is no significant difference in the face of HDAC2 in the hippocampal neurons of the offspring born. However, the expression of HDAC2 in the hippocampal neurons of the adult offspring stressed during pregnancy is decreased, suggesting that the expression characteristics of HDAC2 may play an essential role in the acquired learning and memory function and development (Hou *et al*., 2014) , and its mechanism is related to the inhibition of neurogenesis.

LIAO, L.; CHAI, B. R.; ZHAO, T.; LIU, W.; ZHANG, X.; XU, X.; TIAN, X.; LV, M.; YAO, X. & BAI, S. HDAC2 inhibe la neurogénesis del hipocampo y afecta la función cognitiva en la descendencia adulta estresada prenatalmente. *Int. J. Morphol., 41(3)*:811-818, 2023.

RESUMEN: El objetivo de este estudio fue investigar el mecanismo del estrés prenatal en la función cognitiva de la descendencia y aclarar el cambio de la expresión de la histona desacetilasa 2 (HDAC2) en las neuronas del hipocampo de la descendencia. 16 ratas SD preñadas se dividieron aleatoriamente en un grupo de control y un grupo de estrés, con ocho ratas en cada grupo. El grupo de estrés recibió estrés durante 15 a 21 días

de pre, preñez, mientras que el grupo de control no recibió ningún tratamiento. El comportamiento similar a la ansiedad y la memoria espacial, el aprendizaje y la capacidad de memoria se detectaron en campo abierto, laberinto en cruz elevado, prueba de reconocimiento de objetos novedosos y laberinto de Barnes. La tinción de Nissl se utilizó para detectar la función de las neuronas del hipocampo. Se utilizó Western blot para detectar la expresión de la proteína HDAC2 en las neuronas del hipocampo de la descendencia adulta. La tinción de inmunofluorescencia se utilizó para detectar la expresión de la proteína HDAC2 y la neurogénesis del hipocampo. La capacidad de aprendizaje y memoria de la descendencia adulta se redujo. El estrés prenatal dañó la función de las neuronas del hipocampo, se reguló negativamente la expresión de HDAC2 y se redujo el número de neuronas. El estrés prenatal materno puede regular a la baja la expresión de HDAC2 en el hipocampo de la descendencia, inhibe la neurogénesis del hipocampo y deteriora la función cognitiva.

PALABRAS CLAVE HDAC2; Estrés; Deterioro cognitivo; Epigenética

REFERENCES

Anacker, C.; Luna, V. M.; Stevens, G. S.; Millette, A.; Shores, R.; Jimenez, J. C.; Chen, B. & Hen, R. Hippocampal neurogenesis confers stress resilience by inhibiting the ventral dentate gyrus. *Nature, 559(7712)*:98-102, 2018.

Bock, J.; Wainstock, T.; Braun, K. & Segal, M. Stress in utero: prenatal programming of brain plasticity and cognition. *Biol. Psychiatry, 78(5)*:315-26, 2015.

Dhanushkodi, A.; Bindu, B.; Raju, T. R. & Kutty, B. M. Exposure to enriched environment improves spatial learning performances and enhances cell density but not choline acetyltransferase activity in the hippocampus of ventral subicular-lesioned rats. *Behav. Neurosci., 121(3)*:491-500, 2007.

Duman, R. S. Depression: a case of neuronal life and death? *Biol. Psychiatry, 56(3)*:140-5, 2004.

Egeland, M.; Zunszain, P. A. & Pariante, C. M. Molecular mechanisms in the regulation of adult neurogenesis during stress. *Nat. Rev. Neurosci., 16(4)*:189-200, 2015.

Ellman, L. M.; Schetter, C. D.; Hobel, C. J.; Chicz-Demet, A.; Glynn, L. M. & Sandman, C. A. Timing of fetal exposure to stress hormones: effects on newborn physical and neuromuscular maturation. *Dev. Psychobiol., 50(3)*:232-241, 2008.

Grant, J. E.; Fineberg, N.; van Ameringen, M.; Cath, D.; Visser, H.; Carmi, L.; Pallanti, S.; Hollander, E. & van Balkom, A. J. New treatment models for compulsive disorders. *Eur. Neuropsychopharmacol., 26(5)*:877-84, 2016.

Guan, J. S.; Haggarty, S. J.; Giacometti, E.; Dannenberg, J. H.; Joseph, N.; Gao, J.; Nieland, T. J.; Zhou, Y.; Wang, X.; Mazitschek, R.; *et al*. HDAC2 negatively regulates memory formation and synaptic plasticity. *Nature, 459(7243)*:55-60, 2009.

Hausknecht, K.; Haj-Dahmane, S. & Shen, R. Y. Prenatal stress exposure increases the excitation of dopamine neurons in the ventral tegmental area and alters their reponses to psychostimulants. *Neuropsychopharmacology, 38(2)*:293-301, 2013.

Hou, N.; Gong, M.; Bi, Y.; Zhang, Y.; Tan, B.; Liu, Y.; Wei, X.; Chen, J. & Li, T. Spatiotemporal expression of HDAC2 during the postnatal development of the rat hippocampus. *Int. J. Med. Sci., 11(8)*:788-95, 2014.

Kempermann, G.; Kuhn, H. G. & Gage, F. H. More hippocampal neurons in adult mice living in an enriched environment. *Nature, 386(6624)*:493-5, 1997.

Kim, D. R.; Bale, T. L. & Epperson, C. N. Prenatal programming of mental illness: current understanding of relationship and mechanisms. *Curr. Psychiatry Rep., 17(2)*:5, 2015.

Koenig, J. I.; Kirkpatrick, B. & Lee, P. Glucocorticoid hormones and early brain development in schizophrenia. *Neuropsychopharmacology, 27(2)*:309-18, 2002.

McEwen, B. S. & Gianaros, P. J. Stress- and allostasis-induced brain plasticity. *Annu. Rev. Med., 62*:431-45, 2011.

Mirescu, C. & Gould, E. Stress and adult neurogenesis. *Hippocampus, 16(3)*:233-8, 2006.

Monk, C.; Lugo-Candelas, C. & Trumpff, C. Prenatal developmental origins of future psychopathology: mechanisms and pathways. *Annu. Rev. Clin. Psychol., 15*:317-44, 2019.

Mychasiuk, R.; Gibb, R. & Kolb, B. Prenatal stress alters dendritic morphology and synaptic connectivity in the prefrontal cortex and hippocampus of developing offspring. *Synapse, 66(4)*:308-14, 2012.

O'Donnell, K. J. & Meaney, M. J. Fetal origins of mental health: the developmental origins of health and disease hypothesis. *Am. J. Psychiatry, 174(4)*:319-28, 2017.

Osborne, S.; Biaggi, A.; Chua, T. E.; Du Preez, A.; Hazelgrove, K.; Nikkheslat, N.; Previti, G.; Zunszain, P. A.; Conroy, S. & Pariante, C. M. Antenatal depression programs cortisol stress reactivity in offspring through increased maternal inflammation and cortisol in pregnancy: The Psychiatry Research and Motherhood - Depression (PRAM-D) Study. *Psychoneuroendocrinology, 98*:211-21, 2018.

Penney, J. & Tsai, L. H. Histone deacetylases in memory and cognition. *Sci. Signal, 7(355)*:re12, 2014.

Pham, K.; Nacher, J.; Hof, P. R. & McEwen, B. S. Repeated restraint stress suppresses neurogenesis and induces biphasic PSA-NCAM expression in the adult rat dentate gyrus. *Eur. J. Neurosci., 17(4)*:879-86, 2003.

van Praag, H.; Christie, B. R.; Sejnowski, T. J. & Gage, F. H. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc. Natl. Acad. Sci. U. S. A., 96(23)*:13427-31, 1999.

White, A. O. & Wood, M. A. Does stress remove the HDAC brakes for the formation and persistence of long-term memory? *Neurobiol. Learn. Mem., 112*:61-7, 2014.

Wong, E. Y. & Herbert, J. Raised circulating corticosterone inhibits neuronal differentiation of progenitor cells in the adult hippocampus. *Neuroscience, 137(1)*:83-92, 2006.

Zaba, L. C.; Fuentes-Duculan, J.; Eungdamrong, N. J.; Abello, M. V.; Novitskaya, I.; Pierson, K. C.; Gonzalez, J.; Krueger, J. G. & Lowes, M. A. Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. *J. Invest. Dermatol., 129(1)*:79-88, 2009.

Corresponding author:
Xueping Yao
Key Laboratory of Special
Environment and Health
Research in Xinjiang
Urumqi
P. R.CHINA

E-mail: 55yaoxp@ sina. cn

Shengbin Bai : E-mail: bsbxx@126.com