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Research Article

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Stimulation On Central NR2B NMDA Receptor in Neonatal and Juvenile Rats

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Abstract

Objective: *To observe the excitability of neonatal and juvenile rats (P35~P38) stirred by a strong electrical stimulation, that is registered by the hippocampus and anterior cortex.*

Methods: *The spinal dorsal horn was examined before and after electrical stimulation. The hippocampal CA1 region, the anterior of cerebral cortex and the spinal dorsal horn were subjected to formaldehyde treatment. Immunohistochemistry and western blot were used to analyze the number of FOS protein positive cells in the spinal dorsal horn the hippocampal CA1 region and the anterior cortex of the brain.*

Results: *The sciatic nerve performance of neonatal and juvenile rats was compared with that of adult rats under the same noxious stimulating condition (by strong electrical stimulation). Immunohistochemistry and western blot analysis revealed that LTP and FOS protein were more prominent, but after the application of ifenprodil, these proteins were significantly inhibited.*

Conclusions: *Reducing the stress response induced by peripheral nociceptive stimulation in neonatal and juvenile rats also inhibits the NR2B subunit in NMDA receptors.*

Introduction

Injury stimuli cause acute pain in individuals. If not well controlled, some patients may develop a chronic pain, which could last for several months or even years, and interferes with the physiological and psychological functions of the patient to varying degrees, causing serious complications. Neuralgia (nerve injury-related inflammation) is one of the major causes of chronic pain in the United States, with 22.5% stemming from surgery the more severe the acute pain is after surgery, the higher the probability of postoperative chronic pain [1]. Previous investigations have found that postoperative injury-related pain can lead to central sensitization and is one of the key reasons for the development of chronic pain [2,3]. Therefore, research and control of spinal dorsal horn sensitization in rats is pain and anesthesia. NMDA receptors in the central nervous system, which contains various NR2A/NR2B subtypes occurring in various locations and at different time in rats, are becoming the focus of attention in Juvenile rat studies [4-6]. The aim of this experiment was to assess the NR2A/NR2B subunit performance in juvenile rats compared to adult rats, evaluate LTP-induced differences in the spinal dorsal horn, prefrontal cortex (sensory cortex), and hippocampal CA1 region, and study the role of NVP-AAM077 and/or ifenprodi and FOS protein through western blot analysis to help understand the early memory of developing central nervous systems and their response to pain and treatment with medication [7-9].

Materials and Methods

Animals and Grouping

42 (SPF grade) healthy Sprague-Dawley rats were selected for this study, and the experiments were performed at the Experimental Animal Center (ABSL-3) of the Wuhan University Medical College. We complied with the Ethical guidelines as stipulated by the Animal Ethics Society. A complete ethics review was done and an animal qualification certificate and a license number (SCXK (E) 2015 ~ 0013) granting permission for our study using animals were issued. Rats were partitioned into two groups: a neonatal and juvenile group (35 to 38 days old males weighing 50g to 65g, n=15) an adult group (90 to 100 days old males weighing 185g to 250g, n = 15).

Electrophysiological Experiments in the Spinal Cord, Hippocampus, and Cerebral Cortex

The hippocampus and spinal cord of rats in the neonatal and juvenile adult groups were injected intraperitoneally with 2% of 40 mg/kg pentobarbital sodium for abdominal anesthesia. The head and back were fixed with a brain stereotaxic instrument (Rived holder). The skin was cut at the center and a 1 cm separation of the soft tissue was made. The skull was exposed to reveal the suture; the posterior margin of the left coronal suture of the sagittal suture. Dental drilling and craniotomy were carried out. Needles were used to pick up the meninges, an iris was used for shearing, and the spinal cords T13 ~ L1 laminectomy, L4 and L5 were exposed. The recording electrodes were then extended into the dorsal horn of the spinal cord by 0.1 to 0.5 mm (up to the shallow layers I to II of the spinal dorsal horn). Pancreonium (0.05 ~ 0. 5mg/kg) was administered intraperitoneally to maintain muscle relaxation, and a small animal ventilator was used to sustain breathing (frequency 90 ~ 100 beats/min, tidal volume 5 ~ 20ml). The stimulating hook electrode was placed on the unilateral femoral sciatic nerve and connected to the stimulation output of the microcomputer system. The stainless steel bipolar core recording electrode was inserted into the contralateral cerebral cortex somatosensory region (pre-cortex) (coordinates: adult group AP: 2 ~ 4 mm, L 2 ~ 3 mm, H: 0.5 mm; Juvenile group AP: 1 ~ 2 mm, L 1 ~ 1.5 mm, H: 0.25 mm) and right hippocampal CA1 area (adult group AP: 4.0 ~ 4.4 mm, R: 2 to 3 mm, H: 2.5 to 3 mm; and right hippocampal CA1 area (adult group AP: 4.0 to 4.4 mm, R: 2 to 3 mm, H: 2.5 to 3 mm; Juvenile group AP: 1.5 to 2.5 mm, R: 0.4 ~ 0.8 mm, H: 1.0 ~ 1.2 mm) perform extracellular electrophysiological recording. The RM6240 multi-channel physiological signal acquisition system was used for electrophysiological recording, with a sampling frequency of 8kHz and channel numbers 1, 2, and 4, sensitivity = 25μV, time constant = 0.02s, and filter parameter = 100Hz, 50Hz notch is on). The current intensity was 5V for juvenile rats and 15V for adult rats, and the rest are: a single square with a width of 0.5ms. A wave stimulation was performed every 1 min, lasting 30 min, stimulating the anterior stack 30 times, and the induced peak potential of the ipsilateral thoracic 13 ~ lumbar 1 spinal dorsal horn shallow layer was recorded. Next, there was an HFS stimulation (a current intensity of 10 V in young rats and 30 V in adult rats, 0.5 ms in width, 100 Hz in frequency, 1s in string length, 10s in series, and 4 strings) once every minute for 30 min. The peak value of the peaks of the induced population peaks was recorded as a basic control, and the peaks of the peaks of the A-fiber and C-fiber-induced populations were calculated before the HFS stimulation. One hour after the long-term change was induced in rats, it was completely liquefied by heating with 5-15 g/L of agar (dissolved in water for injection), cooled to 38 °C, poured onto the surface of the exposed spinal cord, and dug once above it. A small well facilitated the administration of a drug solution on the surface of the spinal cord, and NVP-AAM077 (0.025 mg/ml, diluted at 38 °C for injection, followed by the same) or ifenprodil (0.5 mg/ml) (produced by TOCR I, USA) was added drop-wise; 0.3 ml to the juvenile group and 1 ml to the adult group.

Hematoxylin-eosin (H&E) Staining

The spinal cord (L2-3) the hippocampal CA1 and the anterior of cerebral cortex specimens were isolated and fixed in 4% paraformaldehyde for 1-2 days. Then, 4-μm paraffin sections were prepared. After dewaxing, the samples were stained with hematoxylin, differentiated with 0.5-1% hydrochloric acid alcohol and rinsed with tap water for 10 min. Then the samples were further stained with eosin. After dehydration with 75%, 85%, 95%, and 100% alcohol, the sections were cleared with xylene and sealed with neutral gum. H&E staining was performed to examine the morphology of the spinal cord, hippocampus, and cerebral cortex specimens. The nuclei were dyed bright blue by hematoxylin, the cytoplasm was dyed pink by eosin, and the eosinophilic granules in the cytoplasm were bright red with strong reflectivity. The color of the eosinophilic granules in the cytoplasm got deeper by electrical stimulation but lighter after drug treatment. Magnification factor: 50x for the left images and 200x for the right images. Scale bars: 100 μm or 25μm.

Immunohistochemistry

FOP protein examination in the neonatal and juvenile adult groups were randomly divided into: blank control group (n=3); 1 hour after tonic electrical stimulation group (n=3); 3 group after electrophysiological experiment: 2 hours after electrical stimulation, electricity 1 hour after stimulation + NVP-AAM077 observation 2 hours group, 1 hour after electrical stimulation + ifenprodil observation 2 hours group; with 0.9% NaCl 20 ~ 100ml and 10% formaldehyde solution about 100ml (newborn group) and 200ml (In the adult group, the animals were subjected to left ventricular perfusion. After fixation, the thoracic 13 to lumbar 1 spinal cord was extracted and stored at 4 °C for one week. It was embedded in paraffin post-storage, and 4 μm thick paraffin sections were cut and routinely dewaxed with water. One anti-second antibody was diluted to a concentration ration of 1:100, and used for immunohistochemical detection of the c-fos protein. A positive control group and a negative control group were set during staining (no primary antibody was added). Three samples of the anterior cortex, hippocampal CA1 area, and spinal cord section of each animal were used. Three high-power fields (SP×200) were randomly selected from each section. HE staining was used to determine the positive FOS protein area. A brownish yellow area was used as a positive reaction zone.

Western Blot

The spinal cord (L2-3) the hippocampal CA1 and the anterior of cerebral cortex specimens were homogenized in liquid nitrogen, and the total proteins were extracted. After quantification, the proteins were heated with Laemmli sample buffer and further separated (35 μg per lane) using SDS-PAGE. After membrane transfer, the blots were incubated with primary antibodies [primary antibodies used for immunohistochemistry, as well as the mouse anti-GAPDH monoclonal antibody (Cat. #66009-1-Ig, Proteintech); all 1:1000] over night at 4ºC. After washing with PBS, the blot was further incubated with HRP-conjugated goat anti-mouse IgG (H+L) (Cat.SA00001-1, Proteintech) or HRP-conjugated goat anti-rabbit IgG (H+L) (Cat.SA00001-2, Proteintech) for 30 min at 4ºC. Chemiluminescence signals were developed using an ECL kit and the captured with GE ImageQuant LAS 4000mini Biomolecular Imager (GE Healthcare Life Sciences, USA). The images were further processed and analyzed using ImageJ 8.0.

Statistical Analysis

The experimental data were processed by the SPSS18.0 statistical software and results were expressed as mean ± standard error (mean ± SEM). The electrophysiological part was used to conditionally electrically stimulate the pre-spinal spinal dorsal horn, and the hippocampus and anterior cortex induced population peak potential A. The amplitude of the class and/or C nerve fiber wave is the index, and the average data is 30 times the standard; this data was plotted using the software Sigmaplot 8.0. The HE staining and immunohistochemistry data were analyzed with the ImagePro plus 6.0; the red staining area and the IOD value of the positive expression area of FOS protein were analyzed. Western blot data of the band expression of FOS protein expression were examined with the ImageJ software. P <0.05 was considered statistically significant in each group.

Results

Electrophysiological Observation

Electrophysiological observation of changes in the synaptic plasticity of the sciatic nerve of the spinal cord, hippocampus, and cerebral cortex lower limb sensory regions in juvenile and adult rats were made. An increase in the surface of the spinal cord increases the levels of NMDA receptor subunits N2RA and N2RB, but the use of blockers, NVP-AAM077 and ifenprodil changes the level of LTP in the sensory areas of the lower limbs of the spinal cord, hippocampus, and cerebral cortex as seen in Figure 1. Observe that the long-term changes induced by the drug addiction group are inhibited, that is, the subunits of NMDA receptors NR2A or/and NR2B are inhibited, and the changes of NR2A and NR2B can be judged, as well as the synchronization in the spinal cord, hippocampus, and lower limbs of the cerebral cortex. Synaptic plasticity is the change of LTP pattern. Various types of waveforms are judged by their respective incubation periods. Experiments can detect that under noxious stimulation conditions (strong electrical stimulation), the performance of neonatal and juvenile rats is compared with adulthood, long-term potentiation (LTP) is more prominent Results; The juvenile rats reacted mainly to LTP after the strong electric current of type A nerve, but it was significantly inhibited by ifenprodil, p<0.05, and the inhibitory effect of NVP-AAM077 was poor, P>0.05; the adult rats showed that the type C nerve was affected Excitement is the predominant LTP after strong current, which is significantly inhibited by ifenprodil and NVP-AAM077, p<0.05, as shown in Figure 1.

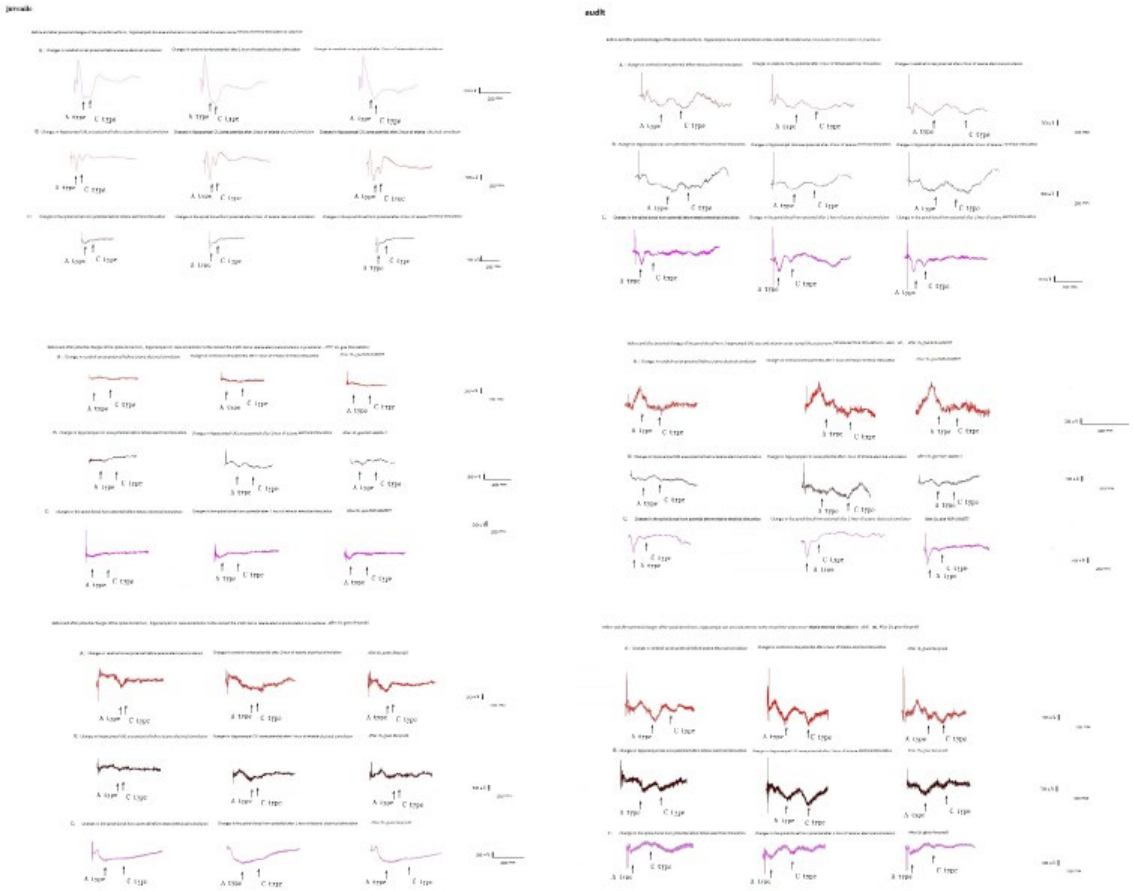

Figure 1: Electrophysiological Experiments Enhances the A-Fiber and C-Fiber-Induced Populations Which is Suppressed by NVP-AAM077 or Ifenprodil Before the HFS Stimulation in the Spinal Cord, Hippocampus and Cerebral Cortex

High-frequency conditioned electrical stimulus was applied to the sciatic nerve of rats (four strings of electrical stimulation: frequency 100 Hz, wave width 0.5 ms, string length 1 s, string interval 10 s; and the intensity of electrical stimulation was set to 15 V, respectively). After the conditioned electric stimulus, a single stimulus of 15 V was applied, and the changes of A-fiber-evoked (or C-fiber-evoked) field potentials in the spinal dorsal horn, and hippocampus, cerebral cortex potential Change were recorded through an RM6240 multi-channel signal acquisition and processing system for at least 60 min. The data were presented as mean ± S.E.M. ($n \geq 3$).

Figure S1: Electrophysiology Examinations Before Tetania
Amplitude change of A-fiber (left panels) and C-fiber (right panels) evoked potential was measured before operation;(A: anterior cortex, B: hippocampal CA1 region, C: superficial spinal dorsal horn).

Figure S2: Electrophysiology Examinations At 60min Post Tetania
Amplitude changes of A-fiber (left panels) and C-fiber (right panels) evoked potential in the spinal dorsal horn, and hippocampus, cerebral cortex potential Change was measured at 60min post operation;(A: anterior cortex, B: hippocampal CA1 region, C: superficial spinal dorsal horn).

Figure S3: Electrophysiology Examinations at 120min Tetania (NVP-AAM077 or Ifenprodil Changes the Level of LTP)
Amplitude changes of A-fiber (left panels) and C-fiber (right panels) evoked potential in the spinal dorsal horn, and hippocampus, cerebral cortex potential Change was measured a measured at 120min post operation;(A: anterior cortex, B: hippocampal CA1 region, C: superficial spinal dorsal horn).

Hematoxylin-eosin (H&E) Staining

Hematoxylin-eosin (H&E) staining of FOS protein observation of the electrical stimulation of the sciatic nerve of the spinal cord, hippocampus, and cerebral cortex of the lower limbs of the juvenile and adult rat FOS protein yielded positive expressions; the patterns were of a large sample and the detailed map shows this expression in the order; anterior cortex, hippocampus, and spinal cord as seen in Figure 2.

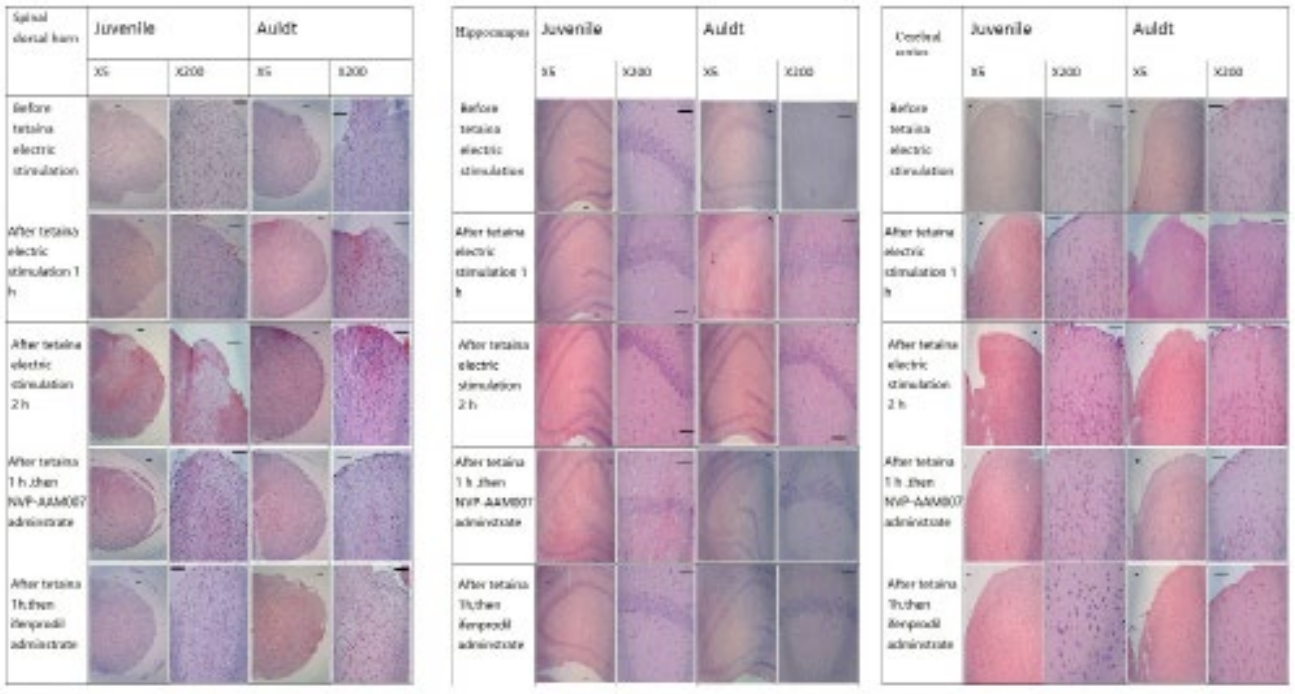

Figure 2: Morphology Change of Spinal Cord Hippocampus and Cerebral Cortex Specimens by Electrophysiological Experiment and NVP-AAM077 or Ifenprodil Treatment

H&E staining was performed to examine the morphology of the spinal cord, hippocampus and cerebral cortex specimens. The nuclei were dyed bright blue by hematoxylin, the cytoplasm was dyed pink by eosin, and the eosinophilic granules in the cytoplasm were bright red with strong reflectivity. The color of the eosinophilic granules in the cytoplasm got deeper by electrical stimulation but lighter after rapamycin treatment. Magnification factor: 50x for the left images and 200x for the right images. Scale bars: 100μm or 25μm.

Immunohistochemistry

Immunohistochemistry was used to observe the positive expression of FOS protein in the spinal cord, hippocampus, and sensory region of the lower extremity of the cerebral cortex and hippocampus of rats by way of electrical stimulation of the sciatic nerve. The pattern was large and detailed, and the order was anterior cortex, hippocampus, and spinal cord, as shown in Figure 3. FOS protein content examination before and after electrical stimulation, reaction neonatal and juvenile rats were inhibited by ifenprodil, and FOS immunopositive cells were lower, $p<0.05$; adult rats were

significantly inhibited by NVP-AAM077 and ifenprodil, and FOS immunopositive cells were all low, $p<0.05$, as shown in Figure 3.

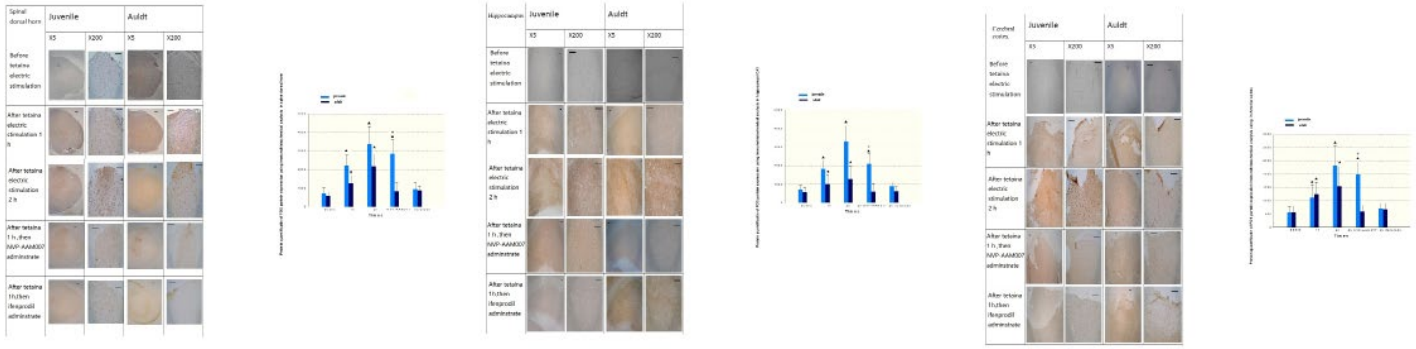

Figure 3: Immunohistochemical Values (IOD values) for FOS Protein in the Neonatal and Juvenile Adult Groups Rats

Immunohistochemistry was used to observe the positive expression of FOS protein in the spinal cord, hippocampus, and sensory region of the lower extremity of the cerebral cortex and hippocampus of rats by way of electrical stimulation of the sciatic nerve. The pattern was large and detailed, and the order was anterior cortex, hippocampus, and spinal cord, as shown in figure 3. The data were presented as mean ± S.E.M. ($n \geq 3$). ▲Compared with the same group, 2h after stimulation (plus NVP-AAM077) and 1 h after stimulation , 2 h after injection (plus ifenprodil), $p<0.01$; ∗compared with the same group, 2h after stimulation (plus ifenprodil) and 1 h after tonic , 2 h after tonic (plus NVP-AAM077), $p<0.05$; # stimulation (same part) comparison, $p<0.05$. Scale bars: 25μm.

Western Blot Analysis of FOS Protein

Western blot analysis of FOS protein was used to observe the positive expression of FOS protein in spinal cord, hippocampus and sensory region of lower extremity of cerebral cortex and hippocampus of rats with electrical stimulation of sciatic nerve in the order of precortical, hippocampal and spinal cord, as shown in Figure 4. neonatal and Juvenile rats are affected by ifenprodil, the FOS protein color is low, and adult rats are affected by NVP-AAM077 and ifenprodil dually. The FOS protein color is low, indicating juvenile the adult rats were inhibited by ifenprodil, $p<0.05$; the adult rats were inhibited by NVP-AAM077 and ifenprodil, $p<0.05$; the rest were all $P>0.05$, which was not statistically significant, see Figure 4.

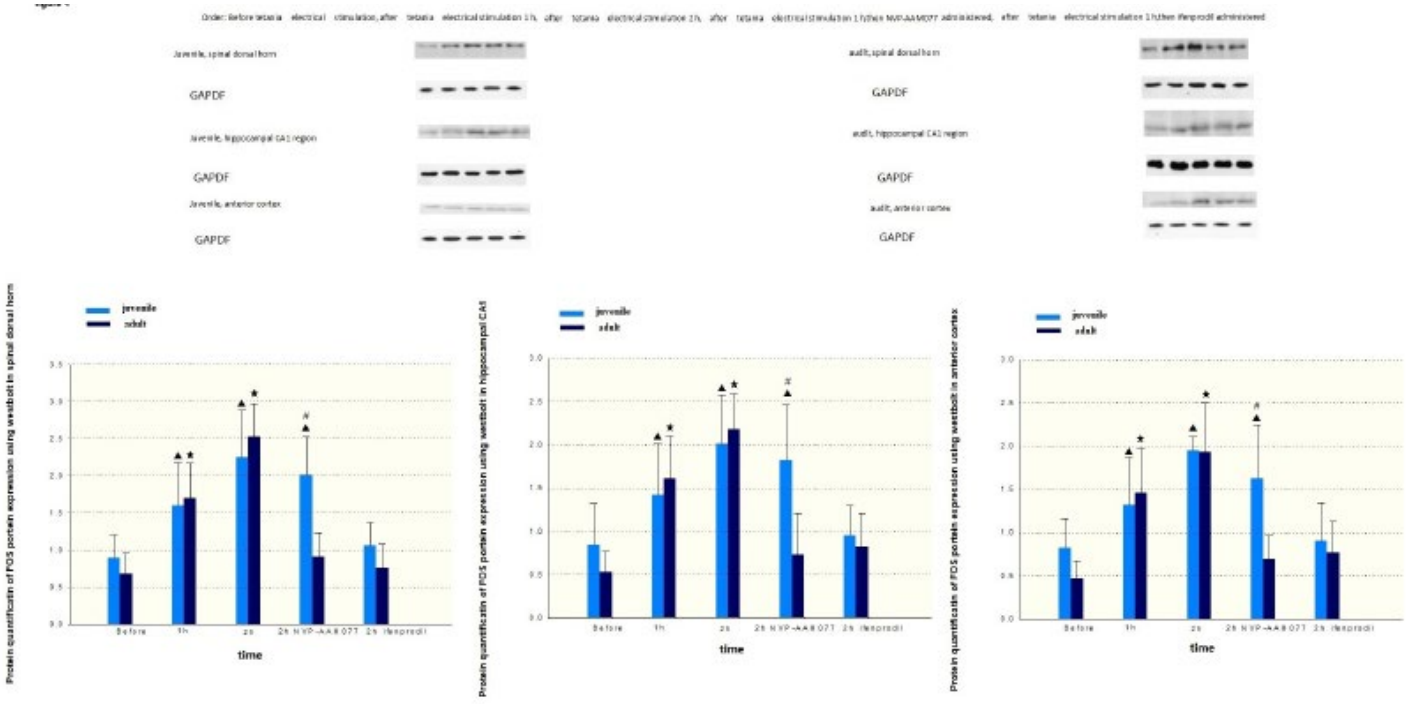

Figure 4: Western Blot Analysis of FOS Protein in the Neonatal and Juvenile Adult Groups Rats

Western blot analysis of FOS protein was used to observe the positive expression of FOS protein in spinal cord, hippocampus and sensory region of lower extremity of cerebral cortex and hippocampus of rats with electrical stimulation of sciatic nerve in the order of precortical, hippocampal and spinal cord, as shown in Figure 4. ▲Compared with the same group, 1h after stimulation, 2h

after stimulation (plus NVP-AAM077) and 2 h after stimulation (plus ifenprodil), $p<0.05$; ∗Compared with the same group, 1h after stimulation, 2 h after stimulation and 2 h after a strong stimulation (plus NVP-AAM077), 2 h after stimulation (plus ifenprodil), $p<0.05$, #stimulation (same part) comparison, $p<0.05$

Discussion

Evoked potential refers to the change of locked potential recorded in the central nervous system when the somatosensory afferent system is stimulated. It has a certain latency, a certain activated or suppressed representative region, and a certain waveform. Evaluate the integrity and functionality of nerve conduction. The evoked potential changes in the central nervous system, including in the spinal cord, hippocampus, and cortex, can reflect whether the conduction function of the spinal cord and spinal cord is stimulated or inhibited. It is an objective and sensitive neuroelectrophysiological index [10,11]. The function of the central nervous system (that is, the function of the neural network), the neuron forms a neural network, via synapses, whose function depends on how the neural excitation is transmitted in the neural network, i.e., between the synapses, spinal cord, and brain are present by the hippocampus, the prefrontal cortex, etc. The formation of the memory loop, pain is accompanied by emotional and memory disorders, the core of which is the imbalance of the inflammatory microenvironment. Therefore, the study of the anterior cortex, hippocampus, and spinal cord can reflect more objectively the development and changes of pain in the body: electricity stimulation in the immature rats as a noxious stimulus through the peripheral nerve of the femoral nerve can cause a strong synaptic plasticity in the spinal dorsal horn, hippocampus, and anterior cortex, but the protective effect of NVP-AAM077 is not obvious. Ifenprodil can, indeed, alleviate the impact of acute pain during treatment in infants and young children, and provides an experimental basis for the formation of the central sensitization of pain.

In childhood, infants and young children respond differently to the spinal cord, hippocampus, and cerebral cortex lower limbs pain; it is different from responses in adult. The electrical stimulation triggers the production and protection of LTP after administration. Characteristics of adult rats. The experiments were performed using a long-term potentiation (LTP) of the nervous system, HE staining, and FOS protein formation, but the FOS protein was widely used to evaluate the body's response to the early formation of stress stimuli, the same noxious stimulus [12]. Under experimental conditions (stimulation of unilateral sciatic nerve), the performances of juvenile rats compared with those of adult rats, and the LTP of cerebral cortex, hippocampus and spinal dorsal horn were examined via HE staining of the eosin staining area, immunohistochemical analysis of the brown area of the FOS protein, and western blot analysis of the FOS protein. A more prominent performance is due to the fact that noxious stimulation, like in adult rats, activates the NMDA pathway, which in turn activates various signaling pathways, including the AMPA pathway, resulting in various physiological effects [13]. NMDA regulates functional changes in the body at different developmental stages of synaptic plasticity; NR2A and NR2B play major roles [14,15].

NR2B is known to play a key protective role in adult rats. Ifenprodil is a typical inhibitor of the NMDA receptor subunit NR2B, while NVP-AAM077 inhibits the NR2A subunit. Our observation of the spinal dorsal horn in juvenile rats confirmed the major role played by the NR2B receptor subunit, the key subunit of LTP that induces pain in the spinal dorsal horn [16]. The ratio of NR2A/NR2B in the spinal dorsal horn is lower, with the proportion of NR2A/NR2B related to development in. It is elevated, which is consistent with the findings observed by other scholars in the hippocampus and cortex [17,18]. Electrical stimulation of the spinal dorsal horn creates hyperalgesia in the anterior cortex and hippocampus, and the selected animal model mimics the irritation of young individuals, with changes occurring in the posterior central nervous system [19].

Neurological development in rats takes place within 21 days after birth, which is equivalent to that in human newborns at months to 1 year old, while 30-day-old rats are comparable to 2-year-old children. The experimental subjects selected for this study were young rats (35~38 days). So, in-depth studies are required to confirm our results of the formation of synaptic plasticity in the dorsal horn of the spinal cord of young adults. The search for effective means of intervention is a major problem in the field of hyperalgesia and abnormal pain research [20].

Conclusion

In conclusion, neonatal Juvenile rats and adult rats were excited by peripheral strong electrical stimulations, which caused spinal nerve fiber excitation that was registered by the hippocampus and anterior cortex. Among them, the A-type nerve fibers in neonatal. Juvenile rats were excited by the stimulation but inhibited by ifenprodil, and the C-type nerve fiber excitation in adult rats was inhibited by both ifenprodil and NVP-AAM077, as revealed by the FOS protein and Western blot examinations. These findings suggest that treatment reduces the nociceptive response caused by electrical stimulation in neonatal Juvenile rats by inhibiting the NR2B subunit of NMDA.

Summary

Treatment reduces the nociceptive response caused by electrical stimulation in neonatal, Juvenile rats by inhibiting the NR2B subunit of NMDA, but in adult rats by inhibiting the NR2A subunit and the NR2B subunit of NMDA.

Source of Funding

This study was supported by the Scientific Research Project of Wuhan Municipal Health and Family Planning Commission (WX15C22).

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the animal ethics review of Hubei Provincial Laboratory Animal Public Service Center and the Center for animal experiment /Biosafety level-III laboratory of Wuhan University. AUP: 2016027.

Authors' contributions

Xueling Chen carried out the studies, participated in collecting

data, and drafted the manuscript. Jie Cheng performed the statistical analysis and participated in its design. Fanli Kong and Hui Xia participated in the acquisition, analysis, or interpretation of data and drafted the manuscript. Jiang Wu is the corresponding author. All authors read and approved the final manuscript.

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