



Antagonistic Effect and Mechanism of Gabapentin on Neuropathic Pain in Rats through P38 MAPK Signaling Pathway

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ABSTRACT

The etiology of neuropathic pain is complex, and the patients are distressed. In order to master more accurate information in the treatment of human nerve tissue and improve the efficiency of treatment, this paper discusses the antagonistic effect of gabapentin on neuropathic pain in rats through the p38 MAPK signal pathway. Thirty-six female Sprague Dawley (SD) rats were randomly divided into three groups, 12 in each group. One group was spinal nerve ligation group (SNL group), gabapentin Group (GBP group, spinal nerve ligation and intraperitoneal injection of gabapentin (50 mg/kg)) and sham operation group (sham group, no spinal nerve ligation, other surgical procedures were the same as SNL group). At 1, 3, 5 and 7 days after operation, the paw contraction latency (TWL) and mechanical paw contraction threshold (MWT) were detected. Then, the expression of Toll-like receptor 4 (TLR4) in dorsal root ganglia was detected by SPSS statistical analysis. Compared with the sham group, MWT and TWL in the SNL group and GBP group were lower at each time point after the operation (all $P < 0.05$). MWT and TWL in the GBP group were higher than those in the SNL group at 5 and 7 days after the operation (all $P < 0.05$). In addition, compared with the sham group, the expression of TLR4 in the dorsal root ganglia of the SNL group was significantly increased ($P < 0.05$), while the expression of TLR4 in the GBP group was not significantly increased ($P > 0.05$). Compared with the SNL group, the expression of TLR4 in the dorsal root ganglion of the GBP group was significantly decreased ($P < 0.05$). Thus, gabapentin combined therapy can effectively reduce the degree of pain in patients with significant efficacy, high safety and fewer adverse reactions.

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Introduction

Neuropathic pain refers to the pain caused by diseases or system damage (1). As the principle behind this pain has not been clearly defined, and the treatment effect is not good from the clinical point of view, so it has attracted more attention (2). The complex pathogenesis of neuropathic pain is the result of the interaction of many factors (3). Because there is no other special treatment, so it seriously affects the quality of life and physical and mental health of patients. However, the methods and drugs used in the diagnosis and treatment of neuropathic pain are not satisfactory, and most patients still suffer from pain (1).

In order to explore the effect of hirudo on the proliferation and apoptosis of vascular smooth muscle cells (VSMCs) in early atherosclerosis rats through p38 MAPK signaling pathway, Arle used a

biochemical analyzer to detect the regulation of leech on the levels of triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C) in blood lipid of rats (2). In addition, he detected the expression of transforming growth factor - β 1 (TGF - β 1) in serum by ELISA, proliferating cell nuclear antigen (PCNA) and apoptosis proteinase-3 (caspase-3) by immunohistochemistry (IHC), and the protein expression levels of mkk3, p38 and c-myc were detected by western method Changes in the aorta. The number of experimental samples selected by Arle is too small to support the conclusion (4, 5). In order to investigate the protective effect of 4-hydroxy-2 (3H) - benzoxazolidone (hboa) on carbon tetrachloride-induced liver fibrosis in rats, Anna used 50% CCl₄ / olive oil intragastric administration for 12 weeks to establish rat liver fibrosis model. At week 8, Anna

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randomly divided the rats into normal control group, liver fibrosis model group, colchicine group and hboa treatment group. Starting from the 9th week, the animals were given drugs every day for 4 weeks, and the changes of serum total protein (TP), albumin (ALB) and hydroxyproline (Hyp) in liver tissue were measured. Finally, Anna detected the expression of α -SMA protein by immunohistochemistry and the expression of MAPK, p-MAPK and p38 protein by Western blotting. Although her experiment can clearly see the protective effect of liver fibrosis in rats, the experimental observation used is not at a specific time, and the results obtained will be different (6). In order to investigate the protective effect of metformin on acute brain injury after brain injury and its mechanism, male SD rats were randomly divided into sham operation group, TBI group, TBI + normal saline group and TBI + metformin group B and TUNEL staining were used to detect neuronal degeneration and apoptosis, and immunofluorescence method was designed to observe the activation of microglia. Then, the mRNA and protein expression levels of proinflammatory factor - α (TNF - α), interleukin beta (IL-1 β), interleukin-6 (IL-6) were detected by real-time quantitative reverse transcription polymerase chain reaction (qPCR) and enzyme-linked immunosorbent assay (ELISA)(7). Finally, the expression of NF - κ bp65 and phosphorylation of ERK1/2 and p38MAPK were detected by Western blot. Moulin's experiment is more focused on the selection of experimental equipment, so it may cause the experimental accuracy is not enough (8, 9). In order to study the effects of Houutuyniacordata extract on angiotensin-converting enzyme 2 (ACE2) and p38 mitogen-activated protein kinase (p38MAPK) pathway in rats with chronic obstructive pulmonary disease (COPD), Forero *et al.* once randomly divided 60 SD rats into blank group, model group and control group COPD model was established by smoking and lipopolysaccharide (LPS) airway perfusion in the control group. Although the effect of Forero *et al.* experiment is very good, we should use some other reagents to get the best control (10).

In this paper, 36 female rats' neuropathological experiments were carried out. The data obtained from SNL, sham and GBP groups after the experiment were statistically analyzed, and the differences between the

data were compared to illustrate the role of gabapentin in neuropathic pain of rats.

Materials and methods

Experimental Materials

The reagents used in this experiment include Toll-like receptor 4 (TLR4) mouse first antibodies, β -actin antibody and gabapentin. Gabapentin is mainly used to prepare a normal saline solution (50 mg/kg) for injection into the mouse abdominal cavity for observation. In this paper, 36 female rats were selected as the research objects. The body weight was 200-220g. The feeding temperature was normal room temperature. Within 24 hours a day, dark and lighting were 12 hours respectively. The use of animals was carried out according to the requirements. At last, 36 rats were randomly divided into three groups, 12 in each group. There was a control group (sham group), SNL group and gabapentin experimental group (GBP group).

Before surgery, the 4-0 chromium sheep intestinal cord was cut into 4-5 cm sections and soaked in sterilized saline for 30 min to make it straight and soft. The skin of the right hind limb of the rat was cut into the middle and posterior part of the thigh, and the sciatic nerve trunk was exposed by blunt separation with curved forceps through the biceps femoris gap. A total of 4 ligatures were made at a distance of about 1 mm. The strength of the ligature was such that the chromium lamb intestine wire could slide over the sciatic nerve trunk, and it was appropriate to see that the peripheral blood flow of the nerve was compressed but not interrupted under the microscope at 40 \times magnification.

Experimental Methods

The control group was treated with gabapentin reagent: the first day's dose was 300mg, which was taken once before going to bed. On the second and third day, it was increased to 600mg, twice a day. The dose was adjusted from day 4 to day 5 by adding 300 mg to reach 900 mg. The frequency of administration was changed to three times a day and the dose was maintained for the other two subsequent days. During the treatment, the rats were closely observed * whether there were drowsiness, retention of urine, vertigo, abdominal distension and so on. On the basis of the control group, the experimental group was

treated with red light therapy. The length of the nerve was set to 13cm, the frequency was 50 Hz, the output length of the wavelength was between (640 ± 10) nm, and the light energy density was 300 mw/cm^2 . The treatment was once a day for 20 minutes, and the time of both groups was 7 days. After treatment, the nerve numbness and sensory abnormalities of the rats were significantly improved, and the nerve pain was also gradually disappeared, indicating that the treatment is effective. If there is no significant improvement in the symptoms of neuropathic pain after the treatment, it means that it is ineffective.

Experimental Data Processing

SPSS is a combined software package with functions of data entry, data classification and data analysis. It can also select modules according to personal needs. The basic functions of the SPSS software package include data management, statistical analysis, chart analysis, data output management, etc. This paper mainly uses the difference of statistical software to test and process the data obtained in this experiment, and the significant difference of data has the following expression. When the two groups of data have the same overall variance but do not know the specific value (Equation 1).

$$t = \frac{\bar{X}_1 - \bar{X}_2 - (\mu_1 - \mu_2)}{\sqrt{\frac{s_p^2}{n_1} + \frac{s_p^2}{n_2}}} - t(n_1 + n_2 - 2) \quad [1]$$

Among them, t represents a significant difference in data, \bar{X}_1 represents the amount of data processing, and \bar{X}_2 represents the amount of data redundancy (Equation 2).

$$s_p^2 = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2} \quad [2]$$

The key to calculating the variance method of the experimental data distribution is to know whether the variance between the two groups of data is the same. The difference is tested by using the F statistic method. The idea of the experiment is to calculate the mean value of different population numbers of samples, and the absolute value of the difference between other sample values and the mean value of samples can be the absolute difference between the

two groups of samples, whether there is a significant difference between the two groups of data can be obtained by one-way ANOVA.

Results and discussion

Statistical Significance of Gabapentin

In this experiment, 36 female rats were randomly divided into three groups. The first group was the spinal nerve ligation group (also known as SNL group), experimental group gabapentin (GBP group) and sham operation group (sham group), with 12 rats in each group. Before the operation, TWL of nerve tissue in the three groups was detected. In the sham group, 12.18, SNL group 11.86, GBP group 12.54, the data between the three groups were statistically insignificant ($P > 0.05$). Compared with the detected data, there was no significant difference in TWL among the sham group, SNL group and GBP group (on day 1 and day 3) ($P > 0.05$). Compared with the sham group, the TWL of the SNL group and GBP group decreased on the 5th and 7th days after the operation ($P < 0.05$). Compared with the SNL group, TWL of the GBP group was significantly increased ($P < 0.05$). The comparison of MWT and TWL of rats in different periods after the operation is shown in Table 1.

Table 1. Comparison of MWT and TWL in Three Group experiment 1,3,5,7 Days

Group	N	1 d	3 d	5 d	7 d
Sham	12	21.5	18.56	20.7	18.68
SNL	12	10.46	8.25	4.2	2.6
GBP	12	10.76	8.5	5.74	4.63

As can be seen in Table 1, there had been a statistically significant decrease in GBP and SNL from 10.46 to 2.6, but the data for the prosthetic segment were relatively stable, with little change from day one to day seven. By comparing the three, it can be seen that the differences are found to be statistically not significant.

In the sham group, SNL group and GBP group, the expression of TLR4 in DRG was 1,1.9,1.2 respectively. Compared with the sham group, the expression of TLR4 in the SNL group showed an upward trend ($P < 0.01$), while in comparison with the GBP group, TLR4 expression did not change significantly ($P > 0.05$). Finally, compared with the SNL group, the expression of TLR4 in the GBP group

decreased significantly ($P < 0.01$). The trend of TLR4 expression among the three groups is shown in Figure 1.

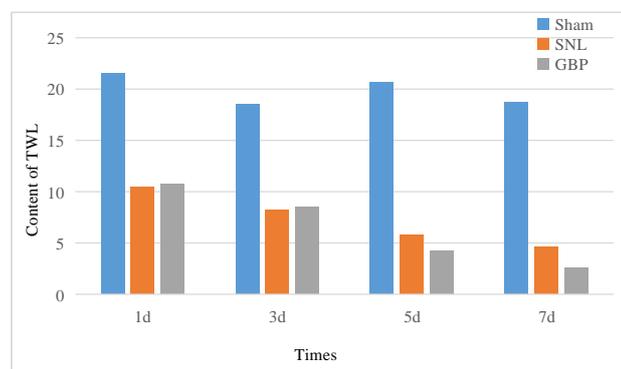


Figure 1. The Trend of the Three Experiments

It is shown in Figure 1, the content of the experimental groups and the trend of the three groups also decreased with time, but the difference between SNL and GBP was not very large and statistically insignificant.

In addition to the normal treatment, the observation group in this experiment was treated with gabapentin capsule orally. The first dose was 300mg once, once a day, the second day: 300mg/time, twice a day, starting from the third day, 300mg/time, 3 times/d. Both groups were given continuous treatment for a period of time, and then the pathogenicity of the two groups of experiments was detected. The effective rate of treatment in the observation group was significantly higher than that in the control group, the difference was statistically significant ($P < 0.05$), the observation effect of the two groups is shown in Table 2.

Table 2. The Comparison of Treatment Effect between the Two Groups

Group	Cured (Cases)	Markedly Effective (Cases)	Effective (Cases)	Ineffective (Cases)	Effective (Cases)
Control Group	14	11	3	8	31
Observation Group	23	7	4	2	34

It can be seen from Table 2 that after the combination treatment of gabapentin on 36 rats, the curative effect is very good, and in the observation group, only 2 cases have no effect, while the control group has 8 cases. Compared with the two, the experimental group compared to the control group, the role is much greater.

After treatment, the expression of NFDS in the observation group in the control group was used to determine the therapeutic effect of gabapentin. When the score of CMS was higher than that of the control group, the data difference between the two groups was statistically significant ($P < 0.05$). The statistical results are shown in Figure 2.

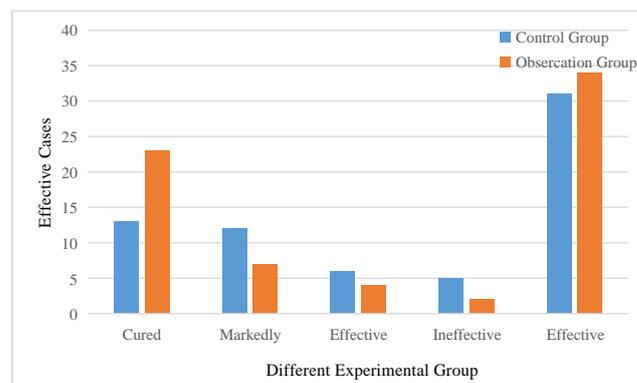


Figure 2. The Difference between the Two Groups of Experiments

As can be seen from Figure 2, we can clearly see the difference between the two groups of experiments, among them, it was shown that gabapentin is effective in the prevention of neuropathic pain, which can increase the healing effect more effectively, reduce the pain of patients, and also has an essential significance in improving the quality of their lives.

Dependent Inhibition

The intrathecal injection of GBP reagent in the experimental rats began to show effect after 20 minutes and the most obvious effect was to inhibit the spontaneous foot contraction reaction (i.e. long-term spontaneous pain) at 40 minutes. Then, the rats in the control group were treated with three different doses of GBP (12, 15, 20 μg), respectively. The consciousness and activity of the rats were not lost or hindered, and the spontaneous foot retraction reaction was obviously inhibited, indicating a dose-dependent manner. We found that the number of foot retraction responses of rats to different doses of GBP was significantly reduced in 7 time periods on day 1 and day 7. Therefore, the dependence of rats on gabapentin is shown in Figure 3.

It can be seen from Figure 3 that the effect of GBP reagent is also improving with the increase of time,

which also shows that gabapentin has an obvious effect on neuralgia.

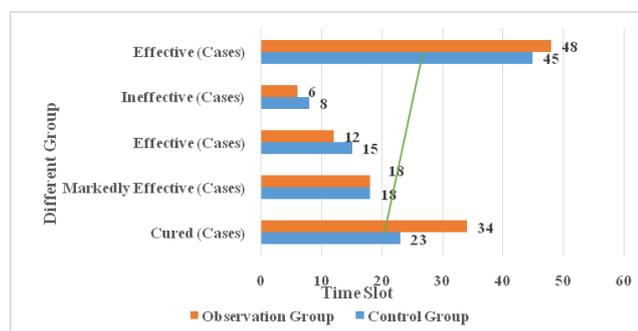


Figure 3. The Effect of GBP

After the intrathecal injection of GBP for 30 min, the effect of GBP began to be obvious, and the effect of inhibiting spontaneous foot contraction (i.e. long-term spontaneous pain) was the most significant at 60 min. The experimental rats were treated with 10, 15 and 20 μ g of GBP in their sheaths respectively, which showed that the times of foot retraction reaction of rats in different doses of the GBP treatment group were significantly reduced compared with the control group. The statistical significance of the three groups of experiments is shown in Figure 4.

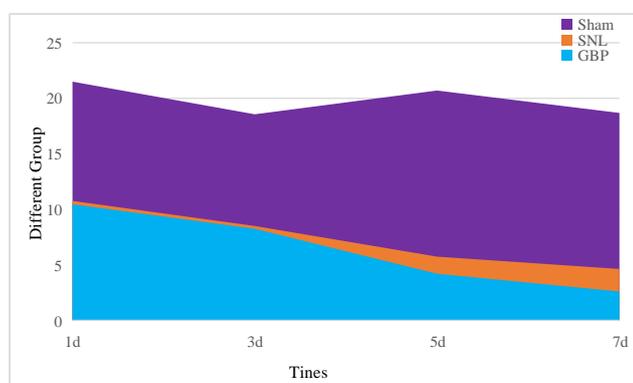


Figure 4. The Area Ratio of Three Different Doses

It can be seen from Figure 4 that GBP has a long-term spontaneous pain inhibition effect in a dose-dependent manner, and the inhibitory effect of GBP on the mechanical pain sensitivity of the PHN rat model is very insignificant. Intraperitoneal injection of gabapentin can relieve the pain caused by spinal nerve ligation and down-regulate the expression of TLR4 in dorsal root ganglia of rats. Gabapentin has analgesic effect on neuropathic pain. In neuropathic pain conditions; TRPA1 expression was increased in

the dorsal root nerve and was consistent with neuropathic pain behavior. After GBP treatment, TRPA1 expression was significantly reduced, suggesting that GBP may play an important role in the regulation of neuropathic pain through TRPA1 receptors.

Activation of glial cells can produce and release large amounts of cytokines, irritative mediators and neuroactive substances, which accumulate around synaptically sensitized neurons and cause further development and persistence of pathological neuropathic pain (5).

Gabapentin, in use in China for a short time, is often associated with a new antiepileptic drug, but it is essentially an analgesic drug for treating neuropathic pain. Gabapentin may be put into clinical first-line analgesic drugs in the past. After oral administration of gabapentin, the intestinal tract will absorb rapidly. The highest blood concentration is 2-3 hours after the patient takes the medicine. However, the blood concentration of gabapentin is not directly proportional to the dose taken by the patient (11, 12).

The absorption pathway of gabapentin in the small intestine is through dispersion and facilitation, so the substance does not affect the bioavailability of gabapentin. The drug has recently been found to respond to multiple pain, i.e. the anti-hyperalgesia and anti-hyperalgesia properties of gabapentin can also be used in postoperative pain (13). Due to its many potential advantages, such as self-metabolism is not being affected by liver and plasma protein and the effect of other drugs on gabapentin is also very small. Therefore, in order to improve the quality of life of patients after surgery, gabapentin will be used frequently in all analgesic adjuvants and narcotic analgesics in the future (14).

Gabapentin works on the α - δ subunit of voltage-dependent calcium channels, and the channels are transported by cell membrane amino acids. After entering the blood, the probability of binding with plasma protein is less than 0.3%. Gabapentin mainly binds across the blood-brain barrier and tissues. Gabapentin has a unique affinity and binding force to brain tissue. The concentration in cerebrospinal fluid and brain tissue was the highest, and the concentration in brain tissue was about 80% of plasma concentration, and the prototype was excreted through the kidney (15).

The receptor of N-methyl-D-aspartate (NMDA) is a ligand-gated ion channel. When activated, NMDA will lead to calcium influx, which will increase the release of excitatory neurotransmitters. NMDA receptor can affect the wind-up of neurons in the spinal dorsal horn. If nociceptive stimulation is induced, the antinociceptive effect of gabapentin can be reversed by D-serine, which can also cause noxious stimulation to the glycine site of NMDA. The binding of the NMDA receptor with gabapentin can antagonize the NMDA receptor and inhibit the activity of the NMDA receptor (16). Although gabapentin has no direct relationship with GABA in nature and does not affect the metabolism and uptake of endogenous GABA, gabapentin can greatly enhance the effect level of GABA receptors in the brain. The enhanced mediating pathway can indirectly reduce excitatory and inhibitory transmission, further produce a central effect, and exert analgesic and sedative effects. Therefore, the GABA receptor is indirectly related to the gabapentin analgesia mechanism (17). When peripheral nerve injury occurs, calcium channels in the dorsal root ganglion of the spinal cord will be up-regulated. If gabapentin concentration reaches a certain level, the inhibition of P / Q voltage may lead to dependence on calcium channels and binding with its subtype proteins (18).

Chronic pain syndrome is the most common clinical neuropathic pain (NeP). Its pain is acute and its incidence rate is high. It has a serious impact on the quality of life of patients. It is defined by the international interest research group's special interest group on neuropathic pain as "pain caused by diseases or lesions directly affecting the body's sensory system" (19, 20).

Its symptoms mainly include stimulating reflex (spontaneous pain, persistent pain) and non-stimulating reflex (hyperalgesia, hyperalgesia). There may also be autonomic nervous dysfunction of the skin, local sensory loss and other symptoms. Many patients with neuropathic pain have intermittent and persistent pain independent of stimulation, which may be tearing pain, burning pain, tingling pain and sympathetic nervous system-dependent activity. Normally responsible for the sensitization and persistent burning in dorsal horn neurons, it is the receptor fiber C that damages spontaneously. Similarly, the large myelin sheath fiber in spontaneous

activity will feel pain and slow response after central sensitization, but it does not rely on stimulation to feel abnormal, because the large myelin sheath fiber does not have any pain under special circumstances (21).

Stimulation-induced pain is a common component of injury and peripheral nerve injury in the clinic. Its key characteristics include abnormal pain and hyperalgesia. When the process of inputting nociceptors is abnormal, it will increase the pain response caused by pain stimulation. This phenomenon is called hyperalgesia clinically. In addition, the sensation caused by harmless stimulation is called abnormal pain. On the one hand, it can be produced by reducing the sensor end threshold of peripheral injury. On the other hand, abnormal pain can also be caused by the change of AB fiber activity in the low threshold myelin sheath of the central nervous system. Since there is no specific mechanism for the clinical diagnosis of abnormal pain, it is more reasonable to classify it as hyperalgesia protection (22).

Among all the means to treat Nep, the main treatment is still drug therapy. Currently, the most common treatment drugs include tramadol, norepinephrine (NE), reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAS), selective 5-HT reuptake inhibitors (SSRIs), capsaicin, calcium channel blockers, 5% lidocaine patch, 5-hydroxytryptamine (5-HT) and opioids. The first-line treatment of Nep includes SNRIs, TCAS and opioids and a little antiepileptic drugs (23).

In recent years, the clinical treatment of neuropathic pain has increased with the development of biotechnology and medical science, especially for chronic refractory Nep. The widely used methods include peripheral nerve electrical stimulation (PNS), deep brain stimulation (DBS), spinal cord electrical stimulation (SCS) and motor cortex electrical stimulation (MCS), among which motor cortex stimulation and spinal cord electrical stimulation (MCS) are widely used. Stimulation is the most widely used method because these two methods can not only improve the quality of life of patients but also have an obvious effect on the treatment of chronic pain syndrome. Although deep brain stimulation has a significant effect on phantom limb pain and peripheral Nep, motor cortex electrical stimulation is also effective in the treatment of intractable neuralgia after

stroke, and the damage is smaller. It can not only significantly reduce hyperalgesia but also relieve more than half of the pain. The effect of peripheral nerve electrical stimulation on single peripheral neuropathy is more obvious, such as radial nerve, common peroneal nerve injury and ulnar nerve injury. For neuropathic pain with no effect or little effect with conventional treatment, nerve electrical stimulation in nerve modulation therapy can play an important role (24).

If the treatment of Nep with drugs does not achieve the desired effect, it can be considered to use the combined nerve block method when necessary. A peripheral nerve block can also treat pain syndrome in complex regions, not only can reduce the pain, but also can reduce the number of drug use, thereby reducing the side effects of drugs and improving the quality of life of patients. In addition, spinal cord electrical stimulation and percutaneous electrical stimulation can also be used to treat patients with relatively fixed neuropathic pain at the pain site. The former way is to stimulate the posterior cord of the spinal cord to make the retrograde impulse and anterograde pain impulse collide. In this way, the gate control system in the posterior horn of the spinal cord can be activated and the pain upload can be blocked. The analgesic effect of the latter is due to the activation of endogenous opioid peptides and the stimulation of coarse nerve fibers at the pain site (25, 26).

MAPK plays an important role in the regulation of mitogen/mitogen kinase (MAPK), which also plays an important role in the regulation of cell proliferation (27, 28). P38MAPK (also known as *cbp*, *mhog1*, *rk* and *sapkz*) is a classic mammalian MAPK signaling pathway. This pathway of signaling is also a key member of MAPK. It functions not only in various influences of inflammation and cellular stress responses but also in cell death by survival, differentiation and evaporation. It is generally considered as the transition point of the cell signal pathway (29, 30).

The activation of MAPK is mainly accomplished by the phosphorylation of tyrosine (T) and threonine (Y) in the trichoryl "TXY" on the surface of a T-loop or loop-12 structure close to the activation site. The key structure of MAPK activation is determined by T. Among them, amino acids can separate two

phosphorylation sites, and the x-point of different MAPKs is different, which leads to the different lengths of the T-loop. In the p38 subfamily, all of them have "tgy" double site phosphorylation module (JNK is "TPY", ERK is "tey" module), and there are six amino acids less than others, such as the L12 site of the kinase (RAS / ERK, JNK / SAPK), and the phosphorylation of p38 molecule is different from the above two (31, 32). In addition, the activation and inactivation of p38 α can be recorded by X-ray crystallography, which is very helpful for people to understand the specific substrate of p38 (33).

In this study, we observed that after the model was established, MWT decreased and TwL shortened in the left hind limb of rats, indicating that the model was successfully reconstituted, and after the administration of GBP, MWT increased and TwL prolonged, indicating that GBP has a certain therapeutic effect on post-CCI neuropathic pain; however, with the prolongation of time, MWT and TwL of rats could return to the preoperative level, indicating that the treatment of post-CCI neuropathic pain by GBP TRPA1 channel is a functional protein of injurious stimulus perception, localized in peptidergic neurons, which selectively regulates inflammatory nociceptive hyperalgesia, and both heat and mechanical friction can affect TRPA1 channel protein-coding. In conclusion, we suggest that GBP can treat post-CCI neuralgia; meanwhile, TRPA1 may be involved in the analgesic mechanism of gabapentin.

Conclusion

In recent years, the improvement of medical technology in many places is very concerned, and the level of medical treatment has also been greatly improved, but in some areas, it is still a point that has not been broken. Just like nerve pain, because neurons are particularly sensitive and extremely complex, if doctors do not have enough experience and high-quality technology in the treatment, it will lead to tragedy. In this case, we should first see the pathogenesis and nature of the disease. Only by understanding the most essential characteristics of this thing can we better formulate treatment measures. Then, under the study of the nature of the disease, we can carry out the innovation of science and technology

and medical technology, and then we can cure the patients better.

The effects of the p38 MAPK signaling pathway on the nerve tissue of 36 rats were studied. Thirty-six female rats were randomly divided into three groups. The first group was the spinal nerve ligation group (SNL group), experimental group gabapentin (GBP group) and sham operation group (sham group), with 12 rats in each group. In this paper, we registered the neuropathic pain of rats before the experiment, and then compared the inhibitory effect of gabapentin on nerve pain in rats. Then SPSS statistics was used to analyze the observed phenomena. By comparing the conclusions obtained, by comparison, we can clearly understand that the nerve pain of rats before the experiment is very sensitive, and after the drug, the inhibition effect on pain is great.

The study of gabapentin's antagonistic effect on neuropathic pain in rats provides us with a very good experimental experience in understanding people's neurological diseases from the perspective of neurons, and also provides very important information for the treatment of neurological diseases in the medical field, and is also of great help in the prevention. It is a very important challenge that how to test the nerve pain of rats smoothly, so as to improve the therapeutic effect of this kind of treatment.

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None.

Interest conflict

None.

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