Effect of Taspine hydrochloride on the repair of rat skin wounds by regulating keratinocyte growth factor signal

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ABSTRACT
To explore the regulation of keratinocyte growth factor (KGF) in the process of repairing rat skin wounds by taspine hydrochloride (TA/HCL), 45 male Sprague-Dawley (SD) rats were purchased and divided into an experimental group, a dimethyl sulfoxide (DMSO) control group, and a basic fibroblast growth factor (bFGF) control group, each with 15 only. A back trauma model was innovatively adopted to prevent rats from biting and contaminating. The wound healing time and healing rate of the rat, and the Hydroxyproline (Hyp) and KGF expressions were observed. Morphological changes of wound tissue and the number of capillaries were observed after hematoxylin-eosin (HE) staining. The results showed that wound healing rate of experimental group and bFGF group was significantly higher than that of DMSO group \((P < 0.05)\) after 2–15 days, and wound healing time of experimental group was 18 days, which was significantly lower than that of the DMSO group \((P < 0.05)\). Expression levels of Hyp and KGF in the granulation tissue of rats in the experimental group were much higher than those in the DMSO control group after trauma \((P < 0.05)\). In early stage of wound tissue repair, the number of new capillaries formed in experimental group was significantly higher than that in DMSO control group \((P < 0.05)\). In summary, this study innovatively focused on KGF. The mechanism of TA/HCL promoting rat skin wound healing was closely related to KGF.

1. Introduction
With economic development and social progress in recent years, the number of traumatized people has become larger and larger, and people have paid more and more attention to and discussed the wound repair. As the largest external organ in the body and the first barrier to protect the body, the skin is most vulnerable to trauma [1]. Skin wounds repair refers to the interaction of various proliferating repair cells, intercellular substance, and growth factors after skin injury, filling and connecting the damaged tissues, thereby completing the complex dynamic process of self-repair [2–4]. This process usually needs to manage three development periods, namely: hemostasis and inflammation period, cell proliferation and differentiation period, and damaged tissue reconstruction or scar formation period [5]. In the first stage, after skin injury occurs, blood vessels will contract immediately, and various hemostatic factors, fibrin, and platelets will aggregate to complete the hemostatic process. At the same time, platelet degranulation will release various chemokines, attracting leukocytes and other inflammatory cells to gather and trigger an inflammatory response [6]. In the cell proliferation and differentiation stage, epithelial cells secrete various growth factors to promote cell proliferation, and many fibroblasts proliferates to form granulation tissue as the intercellular substance to promote the connection between cells [7]. Finally, the intercellular substance rich in fibrin and collagen III is constantly renewed into extracellular matrix dominated by collagen I to complete the wound reconstruction process [8–10].

Epithelial cells play an important role in wound healing and wound scar tissue formation. As a type of epithelial cell-related specific growth factor,
keratinocyte growth factor (KGF) is also closely related to the wound repair process [11]. KGF is an important part of the fibroblast growth factor (FGF) family, also known as FGF-7. The molecular size of KGF is about 26–28 kDa, composed of 163 amino acids, and contains only one peptide chain [12–14]. Mesenchymal cells usually release KGF in a paracrine manner. Free KGF is recognized by specific receptors on the surface of epithelial cells and binds to it. It plays a role in the repair of skin wounds. Keratinocyte growth factor receptor (KGFR), as the specific receptor of KGF, is widely distributed on the surface of epithelial cells [15–17]. In addition, KFG is also closely related to tumor formation and development, embryonic development, etc., and is a growth factor with multiple functions [18]. Studies have found that KGF plays an important role in wound healing. Lots of KGF appears in the tissue during the healing process, which stimulates the vitality of keratinocytes and induces a large number of proliferating cells to migrate to the wound part, thereby achieving wound repair [19]. Transfection of KGF plasmid into sepsis and diabetic mouse cells by electrottransformation can promote epithelial formation and skin wounds repair in these mice [20–23]. Constructing an adenoviral vector expressing the KGF gene allows the wound site to express a large amount of KGF protein, which can also promote the rapid completion of angiogenesis and wound repair in the wound site [24].

Taspine is extracted and isolated from the rhizomes of Paeonia, a plant of the genus Paeonia in the Berberis family, and is commonly used in the folk to treat bruises and arthritis [25]. Studies have found that taspine has a strong affinity with vascular endothelial cells and fibroblast membranes, as well as anti-inflammatory effects and promoting wound healing functions, but the mechanism of its action has not been elucidated [26]. The structural formula of Taspine contains two lactone ring structures and belongs to the apophyllitic alkaloids. Studies have shown that Taspine has a variety of pharmacological effects, including antibacterial, wound repair, anti-inflammatory, antiviral and cytotoxic effects [27]. Applying Taspine to a mouse model of tuberculosis can significantly inhibit the replication of Mycobacterium tuberculosis; Taspine has a significant anti-inflammatory effect in arthritis and granulomas; and Taspine can also inhibit the growth of oral cancer cells and inhibit the replication of related tumor viruses, and exert its powerful cytotoxic and antiviral effects [28–30]. Some studies have applied Taspine Hydrochloride (TA/HCL) to the treatment of wounds, and found that it can promote the migration of fibroblasts, thereby promoting the rapid repair of skin wounds. At the same time, KGF was detected in the process [31].

This study innovatively focused on the relationship between TA/HCL and KGF to verify whether TA/HCL can regulate the KGF signal to achieve the repair effect on rat skin wounds. Forty-five male Sprague-Dawley (SD) rats were purchased from Liaocheng People’s Hospital and divided into an experimental group, a DMSO control group, and a bFGF control group, with 15 rats in each group. A bilateral trauma model was established on the back of the rat, thereby avoiding the infection and influence caused by the biting of the rat during the experiment. They were treated with TA/HCL, DMSO, and bFGF to observe the healing time and wound healing rate of the rat's wound. The kit determined the expression of Hydroxyproline (Hyp) and KGF at each time after treatment. Hematoxylin–eosin (HE) staining was performed to observe the morphological changes and the number of capillaries in the wound tissue. In addition, the repair effect of TA/HCL on rat skin wounds and the influence on KGF were comprehensively evaluated, so as to explore the regulation effect of KGF in the process of TA/HCL repairing rat skin wounds.

2. Materials and methods

2.1 Experimental animals

The SD rats used in this experiment were all purchased from Liaocheng People’s Hospital. They were all males and weighed about 250 g. They were raised in a ventilated and clean animal laboratory. During the experiment, all treatments of SD rats were strictly implemented in accordance with the national laboratory animal regulations. This animal experiment had been approved by the experimental animal ethics committee.

2.2 Main reagents

TA/HCl was purchased from Shanghai Yuanye Biotechnology Co., Ltd., DMSO was purchased from Changzhou Lier Chemical Co., Ltd., Hyp test
kits were purchased from Shanghai Qiuyuan Biotechnology Co., Ltd., and KGF enzyme-linked immunosorbent assay (ELISA) kits were purchased from Shanghai Fantai Biotechnology Co., Ltd.

2.3 Establishment of rat skin wounds model

A rat skin trauma model was established according to the method in the reference [32]. The rats were fixed and anesthetized by intraperitoneal injection of 2% sodium pentobarbital. The standard dosage was 30 mg/mL. After the rat was performed with anesthesia, the back was depilated. After alcohol was disinfected, two circular wounds were made on the depilated part of each rat with a special puncher. The diameter of the wound was about 1.6 cm. After the superficial skin was cut, it had to ensure that the wound was deep enough. Subcutaneously, the establishment of the mechanical injury rat model was completed, and the wound of the rat model was exposed without any treatment to ensure that the rat was kept in a single cage.

2.4 Drug treatment plan

The rat models were divided into three groups, each with 15 skin wounds model rats. Rats in the experimental group were treated with TA/HCl. It meant that 50 μL TA/HCl (concentration 1 mg/mL) was given to the wound on one side of the back, and an equal volume of DMSO was given to the other side. Rats in the DMSO control group were treated with an equal volume of DMSO to one side of the wound, and one side of the wound was untreated. In the bFGF control group, the rats were given with 50 μL of bFGF (2400 U/mL) in one side, the other side was treated with an equal volume of DMSO, each group was given medication with 2 times/d.

2.5 Measurement of wound healing time

The changes of the wound surface after the establishment of the wound model and the administration of the rats in each group were observed, including redness, inflammation, infection, healing, and crusting. The time of repair and healing of the wound of each group were recorded in real time.

2.6 Measurement of wound healing rate

On the 2nd, 4th, 7th, 11th, 15th, and 20th day after the wound, a transparent sulfuric acid film was used to gently stick the wound on the wound surface. At this time, the wound edge was observed and traced, and the wound area was recorded and calculated. It was assumed that $a$ represented the total wound area of rats before treatment, and $b$ represented the wound area after treatment, the wound healing rate was represented by $v$. The wound healing rate of rats in each group was calculated according to the following equation (1):

$$v = \frac{a - b}{a} \times 100\%$$  

(1)

2.7 Determination of Hyp and KGF content

On the 2nd, 4th, 7th, 11th, and 15th day after trauma, 3 rats in each group were sacrificed. Part of the wound tissue was removed and rinsed in normal saline, and the protein in the tissue was extracted according to Hyp test kit and KGF ELISA. The kit instructions were used to determine the levels of Hyp and KGF in wound tissues in each period.

2.8 Measurement on HE staining and the number of capillaries

SD rats were sacrificed on the 4th, 7th, 11th, and 15th days after trauma. The skin of the wounded site was taken and processed in formalin. The paraffin-embedded specimen was cut into 5 μm-thick sections in a microtome. The paraffin sections were treated with hematoxylin, water, hydrochloric acid alcohol, water, ammonia, water, and eosin in sequence. Then they were washed after alcohol gradient dehydration, and the xylene was transparent and photographed under a microscope for observation.

The number of capillaries in granulation tissue could be determined with below operations. The sections after HE staining were observed using a microscope, and the number of capillaries in the granulation tissue was recorded during the wound healing process of different groups of rats in different periods.
2.9 Statistical analysis

The SPSS software was adopted to statistically analyze the data. Data in accordance with the normal distribution were represented by mean ± standard deviation (mean ± S), t-test was used to represent measurement data, chi-square (χ²) test was used to represent count data, and P < 0.05 indicated that there was a statistical difference.

3. Results

This study was to analyze the repairing effect of TA/HCL on rat skin wounds. It was assumed that it affected the repair process of rat skin wounds by regulating KGF. After the rat back skin trauma model was established, the treatment was carried out with TA/HCL, dimethyl sulfoxide, and bFGF, respectively. The healing time and healing rate on the wound, and the changes of hydroxyproline, KGF, and the number of capillaries were measured to explore the regulation of KGF in the process of repairing rat skin wounds by TA/HCL.

3.1 Test results of wound healing time

The wound healing time of rats in each group was observed after administration. The results showed that the wound healing time of the experimental group was 18 d, which was much lower than the healing time of the DMSO control group (P < 0.05), but there was no significant difference from the bFGF control group (P > 0.05), the specific results were shown in Figure 1.

3.2 Test results of wound healing rate

The wound healing rate of SD rats was calculated on the 2nd, 4th, 7th, 11th, 15th, and 20th day after trauma. The results showed that the wound healing rate of the experimental group and the bFGF group was significantly higher than that of the DMSO control group at 2–15 days. The specific results were shown in Figure 2.

(a-f) Rat wound healing rate results on the 2nd, 4th, 7th, 11th, 15th, and 20th day after trauma.

3.3 Determination of Hyp and KGF in traumatic tissue

The Hyp content in the granulation tissue of rats in different groups was measured on the 4th, 7th, 11th, and 15th day after trauma. The results showed that the Hyp content in the granulation tissue of the TA/HCL group and the bFGF group was higher than that of the DMSO control group, and the difference was significant (P < 0.05). In addition, the TA/HCL test group and bFGF group showed the highest Hyp content on the 15th day after trauma. The specific results were shown in Figures 3–5.

The KGF content in the granulation tissue of rats in different groups was determined on the 4th, 7th, 11th, and 15th days after trauma. The results showed that the KGF content in the granulation tissue of the TA/HCL group and the bFGF group was higher than that of the DMSO control group.
and the differences were significant ($P < 0.05$). In addition, on the 7th day after trauma, the KGF content in the granulation tissue of the TA/HCl group and the bFGF group was the highest. The specific results were illustrated in Figure 6.

### 3.4 HE morphology test results

The wound tissues of each group of rats were observed after HE staining. On the 4th day after trauma, there was still a large amount of necrotic tissue at the wound site in the DMSO control group, and only a few fibroblasts appeared, while a large number of fibroblasts appeared in the bFGF control group and TA/HCl group. Monocytes began to generate fibroblasts and capillaries at the same time. On the 7th, 11th, and 15th day, the granulation tissue of the bFGF control group and the test group grew vigorously. The specific results were given in Figure 7.

### 3.5 Determination of the number of capillaries

The granulation tissue was observed microscopically and the number of capillaries was recorded
Figure 3. Results of Hyp content in granulation tissue on the 4th, 7th, 11th, and 15th days after trauma (DMSO control group).

Figure 4. Results of Hyp content in granulation tissue on the 4th, 7th, 11th, and 15th days after trauma (bFGF control group).

Figure 5. Results of Hyp content in granulation tissue on the 4th, 7th, 11th, and 15th days after trauma (TA/HCl group).
during the wound healing process of different groups of rats at different periods. The results showed that the fibroblasts in the KGF group and bFGF group grow actively in the granulation tissue after trauma, and capillaries appear rapidly in the wound treatment. The number of capillaries in granulation tissue in the last 4–7 days was greatly higher than that in the DMSO control group. The specific results were shown in Figure 8.

(a-d) The number of capillaries in the granulation tissue on the 4th, 7th, 11th, and 15th day after trauma.

4. Discussion

At present, the great progress of society and technology has gradually increased people’s requirements for beauty. The current level and conditions of skin wound repair cannot guarantee the strict requirements of patients. It is caused by a variety of factors (local radiation, paraplegia, and diabetes). The wounds are often difficult to heal, and the number is gradually increasing [32]. According to research statistics, the number of acute trauma patients in the United States can reach more than 1 million in one year, and nearly one-third of trauma patients have to be admitted to the hospital for treatment and care [33]. Therefore, it is imperative to conduct in-depth research on wound repair mechanisms, influencing factors and treatment methods. Both local factors and systemic factors can affect the repair and healing speed of wounds. As one of the local influencing factors, foreign bodies have the most serious impact on wound healing. They often aggravate the inflammatory response and cause the wound repair process
to be slow. Bacteria and other infections also disrupt the wound healing process by enhancing the inflammatory response and protease degradation of the proliferative matrix. In addition, the oxygen demand of the wound site is closely related to the development stage of wound healing, and the initial lack of oxygen can promote the accelerated synthesis of fibroblasts. In the later stage, oxygen is needed to reduce the chance of infection and to ensure the normal secretion of various growth factors. Older and stressed trauma patients will experience delays in all stages of healing, which can be improved by moderate exercise. A variety of factors can affect the healing process of skin wounds, so in-depth exploration of the healing mechanism is particularly important for the treatment of wounds and the prevention of infections.

The healing of skin wounds is a relatively complicated pathological development process, and the granulation tissue formation stage occupies an important position in it. The extent of skin wounds repair, healing speed, and prognostic development are all determined by the quality and quantity of granulation tissue. In this study, the purchased male SD rats were divided into an experimental group, a DMSO control group, and a bFGF control group. A bilateral trauma model of the back of the rat was established. The rat back trauma model can avoid the contamination of the wound caused by the self-biting of the rat during the experiment, and reduce the influence of interfering factors on the experimental results. The three groups of rat back trauma models were successfully established and treated with TA/HCl, DMSO, and bFGF. The wound healing time and wound healing rate of rats were observed. The results showed that the wound healing rate of the experimental group and bFGF group was significantly higher than that of the DMSO control group ($P < 0.05$) at 2–15 days, and the wound healing time was much lower than that of the control group ($P < 0.05$). The protein content in granulation tissue is closely related to the growth of the tissue. In addition, studies have shown that collagen is an indispensable and important
component in the healing process of skin wounds, and Hyp is one of the main components of collagen and occupies a large proportion of collagen. The measured Hyp content can indirectly reflect the collagen content, thus evaluate the progress of wound repair. The results showed that the expression of Hyp in the granulation tissue of rats in the experimental group at 4, 7, 11, and 15 days after trauma was significantly higher than that in the DMSO control group \((P < 0.05)\). The above test results indicated that TA/HCl can promote the repair of skin wounds in rats after acting on the wounded skin of rats. However, the mechanism by which Stapine hydrochloride promotes the healing of skin wounds and whether the healing process is related to the expression of KGF remains to be studied. It was found in this study that the expression of KGF in the granulation tissue of rats in the experimental group at 4, 7, 11, and 15 days after trauma was significantly higher than that in the DMSO control group \((P < 0.05)\). It showed that under the action of TA/HCl, wound repair is accelerated, and the mechanism of TA/HCl promoting injury repair may be related to the large expression of KGF. In addition, the morphological changes and the number of capillaries in the wound tissue were observed by HE staining. It was found that in the early stage of wound tissue repair in rats, the number of newborn capillaries in the experimental group was significantly higher than that in the DMSO control group \((P < 0.05)\), which further confirmed the repair effect of TA/HCl on rat skin wounds. Studies have selected different concentrations of TA/HCl to act on rat models to evaluate the effect of skin damage repair, and found that within a certain range, the higher the dose, the better the effect of damage repair. In addition, there are a large number of KGF receptors on the surface of epithelial cells in skin tissues, and free KGF can be recognized by specific receptors on the surface of epithelial cells and combined with it, thus playing a role in skin wound repair [34,35]. Therefore, in order to further study whether TA/HCl can regulate the

![Figure 8. Results of the number of capillaries in the granulation tissue of rats. Note: * suggested that the difference was statistically great \((P < 0.05)\).](image-url)
KGF signal to repair the rat skin injury, different concentrations of TA/HCl can be selected to observe the changes in the expression level of KGF in the wound tissue in the follow-up experiments. In addition, it will further study the repair mechanism of KGF, so as to carry out more research on the mechanism of skin damage repair.

5. Conclusion

For this study, 45 male SD rats were purchased and divided into an experimental group, a DMSO control group, and a bFGF control group, each with 15 rats. A bilateral trauma model was established on the back of the rat, and treated with TA/HCl, DMSO, and bFGF to observe the healing time and wound healing rate of the rat’s wound. The kit was adopted to measure the expression of Hyp and KGF in each period after treatment, and HE staining was performed to observe the morphological changes and the number of capillaries in the wound tissue. The repair effect of TA/HCl on rat skin wounds and the effect on KGF were evaluated comprehensively. It was found in this study that the wound healing rate of the experimental group and bFGF group was significantly higher than that of the DMSO control group ($P < 0.05$). The expression of Hyp and KGF in the granulation tissue of rats in the experimental group after trauma was significantly increased. The histomorphological results showed that the number of newborn capillaries in the experimental group was significantly higher than that in the DMSO control group in the early stage of wound tissue repair in rats ($P < 0.05$). The results showed that TA/HCl can effectively promote the healing of rat skin wounds, and its mechanism of action may be related to the fact that TA/HCl can promote the massive expression of KGF in injured tissues. The disadvantage of this study were that the sample size was small, and only a single concentration of TA/HCl was selected. In the next step, different concentrations of TA/HCl can be selected to determine the optimal concentration for its repair effect. At the same time, it was for the study of TA/HCl provides a more practical and effective reference value for repairing rat skin wounds by regulating KGF signal. In addition, KGF was expressed in large quantities in the process of wound repair. What specific mechanism has its advantages used to complete the damage repair effect is also a research direction that still needs to be explored in the future.

Highlights

- Taspine hydrochloride has a wound healing effect;
- Mechanism promoting damage repair may be related to the massive expression of KGF;
- Taspine hydrochloride promotes formation of new blood vessels in damaged tissues.

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