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Antipruritic Effect of Matrine

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Short Communication

Pruritus is an unpleasant sensation that elicits the desire or reflex to scratch [1]. As an important physiological response, almost everyone has had experiences of pruritus [2,3]. Moreover, chronic pruritus is a burdensome illness that deeply impairs the quality of life for millions of people every year [4]. Patients with chronic pruritus frequently suffer from concomitant sleep, emotional and cognitive impairments [5]. Since the high prevalence rate (approximately 10% in the general population and even higher in the elderly) and suboptimal treatment regimens, chronic pruritus has become a huge social and economic burden [2]. Inflammatory factors, neuropathic injury, mental disorders and other diseases can cause different degrees of pruritus [6-8]. Histamine has been identified as the key mediator of itch in many clinical conditions presenting with chronic pruritus. However, anti-histamine drugs are not effective for all types of itching [9,10]. For the last decade, although much progress had been made in studies of the neural circuits and molecular mechanisms associated with pruritus, the knowledge of treatment responsiveness in patients with different types of itch is still scarce, especially for patients with histamine-independent pruritus [2]. Hence, new treatments and antipruritic drugs, including traditional Chinese herbal medicines, are becoming a strong desire and an urgent need. More and more researchers have engaged in the field and tried to develop the more effective antipruritic drugs and treatment strategies.

From time immemorial, Chinese had attempted to use herbs to prevent and treat diseases. Nowadays, the utilization of herbs in fact has been considered as an essential branch of traditional medicine. With good efficacy and little side effect, Chinese herbal medicines constitute a potentially pharmacological goldmine. In recent years, we have paid great attention to the mechanisms of traditional Chinese medicine in the relief of itch. We have found that osthole, an active coumarin isolated from herb *Cnidium monnieri* (L.) Cusson, which has been long used in China as an antipruritic herbal medicine, inhibits histamine-dependent itch by modulating TRPV1 activity [11]. However, osthole has no effect on the histamine-independent pruritus, limiting its clinical application.

Our latest research has concentrated on another Chinese herbal medicine, Sophorae Flavescentis Radix (SFR) [12], which has been used in the treatment of viral hepatitis, cancer, enteritis, viral myocarditis, arrhythmia, and skin diseases in China, Japan and some European countries [13-15]. Since SFR has specific therapeutic effects on pruritus and allergic symptoms with less side effects [16,17], it has become an important candidate for researchers in studying antipruritic drugs. It has been reported that SFR inhibits histamine signaling, including the decrease of mRNA levels of both histamine H1 receptor (H1R) and histidine decarboxylase (HDC), as well as the reduction of H1R and HDC activities and histamine content, which may contribute to its allergic effects [18,19]. Also, SFR significantly inhibits serotonin (5-HT)-induced itch behaviors and spontaneous scratching bouts of mice induced by an atopic dermatitis (AD) model in a dose-dependent manner [20]. However, the antipruritic effect of SFR and its underlying mechanisms are still ambiguous. Matrine (MT) is a tetracycloquinolizindine alkaloid from SFR and also its major component. MT exhibits many biological activities and possesses a wide range of pharmacological effects, all of which are similar with SFR. Therefore, MT is an ideal candidate for studying the antipruritic mechanisms of SFR.

Interestingly, we observed that subcutaneous injection of MT not only inhibited the scratching behaviors induced by histamine, compound 48/80 or chloroquine in a dose-dependent manner in C57BL/6 mice, but also relieved the pruritus symptom in chronic pruritus models of atopic dermatitis (AD) and acetone-ether-water (AEW) in C57BL/6 mice. And intraperitoneal injection of MT had a similar antipruritic effect with subcutaneous injection. Since the pruritus induced by chloroquine is histamine-independent, our behavioral experiments suggested that MT exerted antipruritic effects in histamine-dependent, histamine-independent as well as chronic itch.

To evaluate the antipruritic mechanism of MT, we first examined whether the MT inhibited the activity of dorsal root ganglion (DRG), which is an important class of neurons that receive peripheral sensation including itch signal and send it to the spinal cord. The calcium imaging test showed that application of MT did not affect the neuronal activity of cultured DRG neurons, which were isolated from wild C57BL/6 mice. Moreover, MT did not influence the histamine or chloroquine-induced calcium influx in DRG neurons. These results suggested that MT may not directly inhibit the ligand-induced calcium influx in the soma of DRG neurons to relieve itching. We next examined different ion channels on DRG neurons and found that MT inhibited the N-type calcium channel, which plays a vital role in excitatory synaptic transmission. We thus speculated that MT may be involved in the transmission of peripheral itching signal to the centre. We further detected the synaptic activity of superficial neurons in the dorsal horn of the spinal cord slices and found that MT inhibited both spontaneous and evoked excitatory postsynaptic current on the dorsal horn neurons. The results suggest that by suppressing the presynaptic N-type calcium channel, MT inhibits the excitatory synaptic

transmission from dorsal root ganglion DRG to the dorsal horn of the spinal cord.

It is well known that N-type calcium channel is expressed in most of excitable cells, playing an important role in neuronal excitability regulation and neurotransmitter release [21,22]. Thus, lots of blockers for N-type calcium channels have strong side effects [22]. We determined the cytotoxicity of MT by MTT test and found that the MT in its effective antipruritic concentration had no influence on the survival of neurons. In addition, MT (30 mg/kg) of intraperitoneal injection did not affect the rota-rod performance and spontaneous locomotor activity of mice [23], indicating that MT did not influence the motor function. All these results suggest that MT has fewer side effects. Moreover, MVIIA, an antagonist for N-type calcium channel, also has been found to have a significant antipruritic effect. However, drugs such as MVIIA only work when they are administered by intrathecal injection. Compared to subcutaneous injection, intrathecal injection is less convenient and increases the risk of infection, internal bleeding, and spinal cord injury. Our results showed that MT can reach the spinal cord through blood circulation by intraperitoneal and subcutaneous injection. A more convenient route of administration suggests that MT has more advantages as an antipruritic drug.

Conclusion

Chronic pruritus is a disease that is often refractory to the current available medications and seriously compromises the quality of life of patients. As a traditional Chinese medicine, SFR has been widely used in the treatment of chronic pruritus. To further develop and rationally use SFR in the treatment of pruritus patients, the antipruritic mechanism of MT, a major active component of SFR was studied. We found that MT had an anti-pruritus effect similar to SFR in the mouse models of acute and chronic pruritus. It was further proved that the anti-pruritus effect of MT was mediated by inhibiting the presynaptic N-type calcium channel. These findings may provide an important reference and guidance for the clinical application of MT.

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