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Editorial comment

The anti-inflammatory alkaloid *aloperine* in Chinese herbal medicine is potentially useful for management of pain and itch

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In this issue of the *Scandinavian Journal of Pain*, Yang and co-workers report interesting effects of aloperine on acute and inflammatory pain behaviour in mice [1]. Aloperine is an alkaloid isolated from the plant *Sophora alopecuroides L* that, as indicated by preclinical evidence, possesses anti-inflammatory and anti-allergic properties [2]. In the Yang and co-workers' study, aloperine's analgesic efficacies were determined by performing behavioural tests of acute and inflammatory pain, and the authors documented that aloperine can suppress pain-like behaviours in several inflammatory pain models in mice [1].

In acetic acid-induced writhing test, aloperine (40 mg/kg or 80 mg/kg) had an anti-nociceptive effect and reduced the writhing behaviours. However, compared with morphine (10 mg/kg), which almost completely inhibited the writhing response, the effects of these doses of aloperine were minor [1]. Similarly, aloperine was found to be able to dose-dependently suppress formalin-induced pain behaviour, both in the first and second phases, while aspirin was only effective in the second phase [1]. Furthermore, the ear swelling test and carrageenan-induced paw oedema test documented aloperine's suppressing effect on inflammation. In these tests, aloperine was found to suppress the pro-inflammatory cytokines *tumour necrosis factor*, *Interleukin-1 beta*, and *prostaglandin E2*, as well as enhancing the production of anti-inflammatory cytokine *interleukin-10*, in the inflamed tissues [1].

1. Similarities between sinomenine and aloperine, two alkaloids from traditional Chinese herbal medicine

In this respect, the anti-inflammatory effects, aloperine is similar to sinomenine, which is an alkaloid purified from the plant *Sinomenium acutum* that also possesses analgesic efficacy against inflammatory pain behaviour [3,4]. However, unlike sinomenine [5], aloperine failed to illicit any anti-nociception on thermal-stimulated acute pain, assessed by using the hot plate test and the tail flick test [1]. The capability of aloperine to diminish neuropathic pain induced by chronic constriction injury was reported by the same group in 2014, and they proved that the anti-nociceptive effects of aloperine against neuropathic pain is related to reduction of *reactive oxygen species* (ROS) by suppressing the NF-κB pathway in the central nervous system [6]. Surprisingly again, aloperine is similar to sinomenine in terms of analgesic efficacy against neuropathic pain behaviour [3,7] and inhibition of ROS [8].

2. The success of searching for new analgesic substances in traditional Chinese herbal medicine

There are several advantages from studying single molecules isolated from natural, herbal medicines (such as aloperine and sinomenine) as potential drug candidates. The most crucial benefit is that the original herbs have been used for hundreds or even thousands of years, and this indicates that the molecules are well tolerated by humans. As indicated, the clinical safety profiles for aloperine and sinomenine are both positive, with few and relatively mild side effects that are generally reversible [3,9]. Similarly, in the current study the effective dosage of aloperine did not cause any sedation or motor deficit in animals [1], and the same is also true for sinomenine [4]. Beside the issue of toxicity, the drug application routes for molecule from natural medicines are more flexible, since they are usually orally effective, and they can be applied topically. In addition, in majority of the cases, their effective dosage windows are quite broad, which allows the patients to adjust the doses needed without reaching a level limited by toxicity. However, there are challenges as well. It is not easy to identify the site of drug action and the exact drug target.

3. Site and mechanisms of analgesic effect?

It is important to know the action site of a new analgesic; pain modulation is different at different levels of the somatosensory nervous system. In the present study, the authors studied the effect of aloperine on pain-like responses on behaviour of experimental animals to chemical or thermal stimulation. However, Yang and

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co-workers were not able to document where the analgesic effect of aloperine takes place; we do not know if it is peripheral or within the central nervous system. For assessment of the site of action, they could have compared e.g. the analgesic effects induced by peripheral, spinal cord, or intracerebral injections of aloperine. They could have assessed responses of nociceptive neurons at different levels of the neuraxis.

Patients with chronic nociceptive pain often also suffer from depression and anxiety [10]. Therefore, it would be beneficial for chronic pain patients to co-administer drugs that suppress peripheral nociceptors and spinal cord pain relay-neurons, with drugs that improve affective responses to nociceptive stimuli at supra-spinal levels.

For molecules extracted and purified from traditional medicines it is also important to know the exact target; is it a receptor, an enzyme, or a transcription factor? In which cell type(s) does the target reside; is it located in the immune cells or in neuronal cells? When considering combining newly identified analgesic drugs with existing therapies, this is key information for evaluating potential synergy and reduction in side effects from such combinations.

4. Pain and itch are linked in neuronal pathways and aloperine appears to have beneficial effects on both symptoms

Interestingly, aloperine-containing herbal medicine has been widely used in China for treating allergic contact dermatitis, atopic dermatitis, eczema, and other skin conditions with inflammatory components where itching is a major symptom [9,11]. Since the neuronal circuit of itch and pain are related [12,13], and the release of the itch-inducing substance histamine can be suppressed by aloperine during inflammation [2], it is reasonable to expect that aloperine modulates itch in such skin diseases. Pain is a common and often neglected part of the suffering of patients with chronic skin-diseases [14].

To conclude, aloperine, an alkaloid purified from traditional Chinese herbal medicine, has potential to be therapeutic in various pain conditions. Aloperine may be especially beneficial for patients suffering pain and itch from various skin-diseases.

Conflict of interest

The authors declare no conflict of interests.

References

[1] Yang Y, Jin S-J, Wang H-L, Li Y-X, Du J, Zhou R, Zheng J, Ma L, Zhao C-J, Niu Y, Sun T, Li AP, Yu J-Q. Effects of aloperine on acute and inflammatory pain models in mice. Scand J Pain 2015;8:28–34.
[2] Zhou CC, Gao HB, Sun XB, Shi HB, Liu W, Yuan HN, Wang ZX. Antiinflammatory and anti-allergic action of aloperine. Zhongguo Yao Li Xue Bao 1989;10:360–5.
[3] Gao T, Hao J, Wiesenfeld-Hallin Z, Wang DQ, Xu XJ. Analgesic effect of sinomenine in rodents after inflammation and nerve injury. Eur J Pharmacol 2013;721:5–11.
[4] Gao T, Shi T, Wiesenfeld-Hallin Z, Svensson CI, Xu XJ. Sinomenine alleviates mechanical hypersensitivity in mice with experimentally-induced rheumatoid arthritis. Scand J Pain 2015;7:9–14.
[5] Wang Q, Li XK. Immunosuppressive and anti-inflammatory activities of sinomenine. Int Immunopharmacol 2011;11:373–6.
[6] Xu YQ, Jin SJ, Liu N, Li YX, Zheng J, Ma L, Du J, Zhou R, Zhao CJ, Niu Y, Sun T, Yu JQ. Aloperine attenuated neuropathic pain induced by chronic constriction injury via anti-oxidation activity and suppression of the nuclear factor kappa B pathway. Biochem Biophys Res Commun 2014;451:568–73.
[7] Gao T, Shi T, Wang DQ, Wiesenfeld-Hallin Z, Xu XJ. Repeated sinomenine administration alleviates chronic neuropathic pain-like behaviors in rodents without producing tolerance. Scand J Pain 2014;5:249–55.
[8] Qian L, Xu ZL, Zhang W, Wilson B, Hong JS, Flood MP. Sinomenine, a natural dextrorotatory morphinan analog, is anti-inflammatory and neuroprotective through inhibition of microglial NADPH oxidase. J Neuroinflammation 2007;4:23.
[9] Yuan XY, Ma HM, Li RZ, Wang RY, Liu W, Guo JY. Topical application of aloperine improves 2,4-dinitrofluorobenzene-induced atopic dermatitis-like skin lesions in NC/Nga mice. Eur J Pharmacol 2011;658:263–9.
[10] Raja SN, Haythornthwaite JA. Combination therapy for neuropathic pain – which drugs, which combination, which patients? N Engl J Med 2005;352:1373–5.
[11] Yuan XY, Liu W, Zhang P, Wang RY, Guo JY. Effects and mechanisms of aloperine on 2,4-dinitrofluorobenzene-induced allergic contact dermatitis in BALB/c mice. Eur J Pharmacol 2010;629:147–52.
[12] Lagerström MC, Rogoz K, Abrahamsen B, Persson E, Reinius B, Nordenankar K, Olund C, Smith C, Mendez JA, Chen ZF, Wood JN, Wallén-Mackenzie A, Kullander K. VGLUT2-dependent sensory neurons in the TRPV1 population regulate pain and itch. Neuron 2010;68:529–42.
[13] Rogoz K, Andersen HH, Lagerström MC, Kullander K. Multimodal use of calcitonin gene-related peptide and substance P in itch and acute pain uncovered by the elimination of vesicular glutamate transporter 2 from transient receptor potential cation channel subfamily V member 1 neurons. J Neurosci 2014;34:14055–68.
[14] Ljosaa TM, Rustoen T, Mörk C, Stubhaug A, Miaskowski C, Paul SM, Wahl AK. Skin pain and discomfort in psoriasis: an exploratory study of symptom prevalence and characteristics. Acta Derm Venereol 2010;90:39–45.