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Research paper

Huachansu suppresses TRPV1 up-regulation and spinal astrocyte activation to prevent oxaliplatin-induced peripheral neuropathic pain in rats

Yue Hao[a], Xinxin Luo[a], Xiyuan Ba[b], Jiali Wang[a], Shiyang Zhou[a], Shimin Yang[a], Changji Fang[a], Changyu Jiang[b], Wuping Sun[b,*]

[a] School of Pharmaceutical Sciences, Health Science Center, Shenzhen University, Shenzhen 518060, China
[b] Department of Pain Medicine and Shenzhen Municipal Key Laboratory for Pain Medicine, Shenzhen Nanshan People's Hospital and the 6th Affiliated Hospital of Shenzhen University Health Science Center, Shenzhen 518060, China

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ABSTRACT

Chemotherapy-induced peripheral neuropathic pain (CIPNP) is a major dose- and therapy-limiting side effect that is particularly difficult to treat. Huachansu, an aqueous extract from toad skin, is a widely used anti-cancer natural product in China. Clinical findings have established the safety and effectiveness of Huachansu in combination with chemotherapy to promote the therapeutic efficacy while alleviate the side effects, especially cancer-related pain symptoms. Unfortunately, experimental data on the effects and mechanisms of Huachansu in combination with chemotherapy is not available. In this study, the effects of Huachansu were tested *in vivo* on a rat model of oxaliplatin-induced CIPNP. The results show, a single injection of Huachansu 2.5 g/kg produced a short-term analgesic effect on pre-established oxaliplatin-induced CIPNP after 60 min, as indicated by decreased mechanical and thermal hypersensitivity in comparison to oxaliplatin-treated rats. Repeated doses of Huachansu, given during CIPNP induction, prevented the development of oxaliplatin-induced CIPNP. This prophylactic effect of Huachansu was associated with suppressed oxaliplatin-induced TRPV1 up-regulation in the dorsal root ganglia and spinal astrocyte activation. These findings reveal Huachansu therapeutic potential in treating and preventing CIPNP.

1. Introduction

Chemotherapy-induced peripheral neuropathic pain (CIPNP) is the most common and severe side effect of anti-cancer agents including platinum analogs, taxanes, vinca alkaloids and proteasome inhibitors (Park et al., 1900; Argyriou et al., 2012). CIPNP compromises patient's quality of life and is often the main reason for reduced use or discontinuation of lifesaving therapeutic agents. There are currently no effective therapeutic agents to prevent and treat CIPNP.

Platinum derivative oxaliplatin is a widely used first-line treatment for colorectal carcinomas (André et al., 2004). Oxaliplatin causes two types of neuropathic symptoms in human: early acute symptoms characterized by cold-triggered acral paresthesia, and a chronic distal sensory neuropathy that develops after cumulative dose of oxaliplatin (540 mg/m^2 over four cycles or more) (Cersosimo, 2005). Up to 40% of cancer patients who receive platinum agents develop pain and sensory changes (Saif and Reardon, 2005). Recent studies identified the transient receptor potential family of ion channels (TRP channels) as contributors to the induction of CIPNP (Hara et al., 2013; Li et al., 2015). TRPA1 has been identified as a mediator of mechanical and cold allodynia, whereas TRPV1, TRPM8 and TRPV4 are sensitized in DRG neurons in oxaliplatin-induced CIPNP (Anand et al., 2010; Descoeur et al., 2011; Nassini et al., 2011; Chen et al., 2015). Spinal astrocytes and microglia are also involved in the initiation and maintenance of oxaliplatin-induced CIPNP (Yoon et al., 2013; Di Cesare Mannelli et al., 2014; Robinson et al., 2014; Janes et al., 2015; Deng et al., 2016). Oxaliplatin-induced mechano-hypersensitivity in rats is associated with hyperactivation of astrocytes and increased production of pro-inflammatory and neuroexcitatory cytokines (Janes et al., 2015; Deng et al., 2016). The increased cell density of microglia and astrocytes is strongly related to pain hypersensitivity since the glial inhibitor minocycline and fluorocytrate fully prevent oxaliplatin-evoked pain (Di

Abbreviations: ANOVA, analysis of variance; CIPNP, chemotherapy-induced peripheral neuropathic pain; DRG, dorsal root ganglia; DMSO, dimethyl sulfoxide; GFAP, glial fibrillary acidic protein; Iba-1, Ionized calcium binding adaptor molecule-1; i.p., intraperitoneal injection; PBS, phosphate buffered saline; PWMT, paw withdrawal mechanical threshold; TRPV1, transient receptor potential vanilloid 1

* Corresponding author.
E-mail addresses: wupingsun@email.szu.edu.cn, wuping.sun@foxmail.com (W. Sun).

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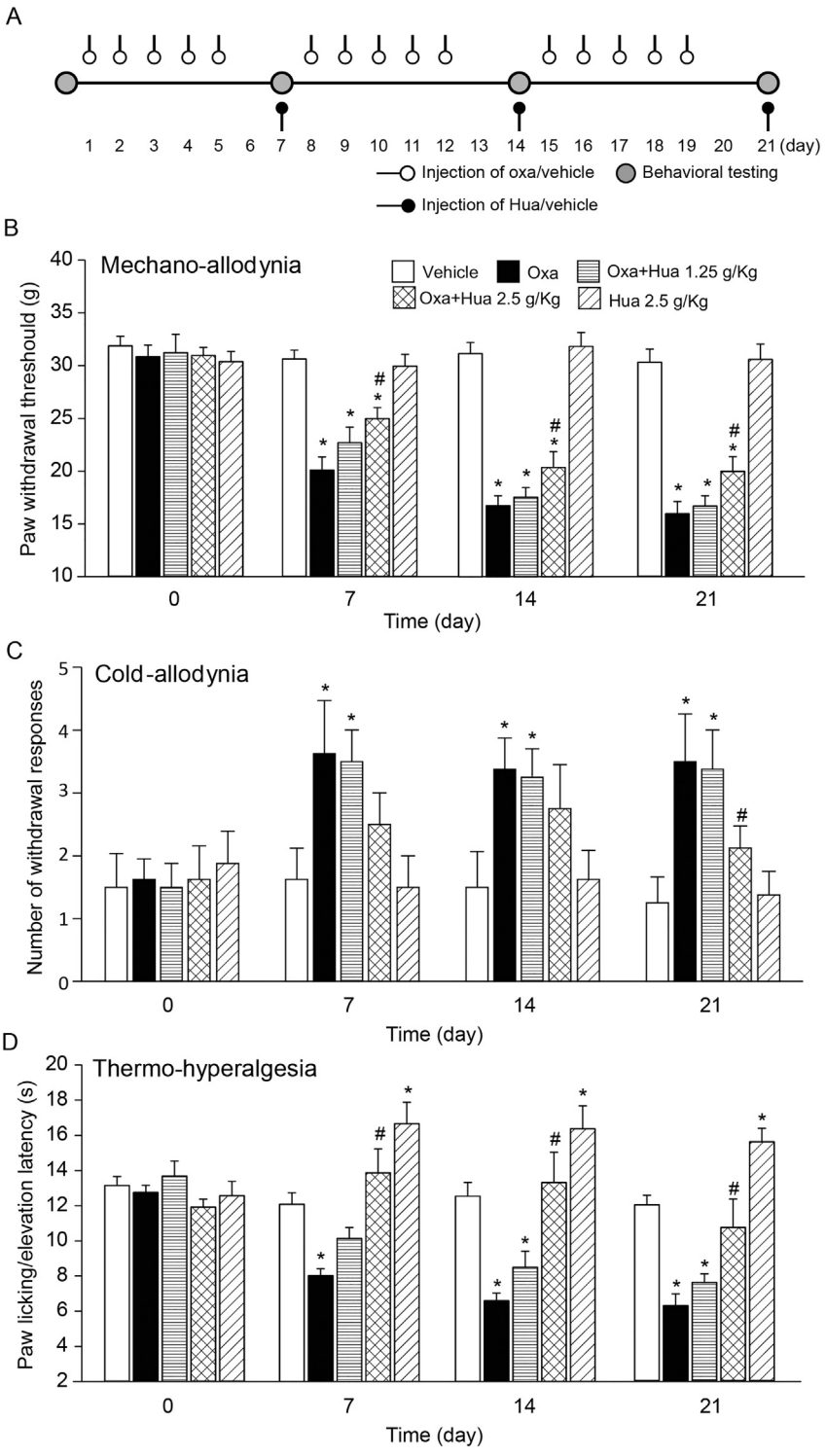

Fig. 1. Alleviation of oxaliplatin-induced mechanical/cold allodynia and thermal hyperalgesia by a single injection of Huachansu.

A The experimental design for Experiment 1. B, C and D Huachansu 2.5 or 1.25 g/kg was administered (i.p.) on day 7, 14 and 21 post first injection of oxaliplatin. Paw withdrawal threshold in the von Frey test (B), number of responses in cold acetone test (C) and paw licking latency in the hot plate test (D) were measured 60 min after the injection of Huachansu. Oxa: oxaliplatin; Hua: Huachansu. Data is expressed as mean ± SEM. *$p < 0.01$ *vs.* Vehicle; #$p < 0.01$ *vs.* oxaliplatin; Repeated measures ANOVA followed by LSD *post hoc* test (n = 8 each group).

Cesare Mannelli et al., 2014).

Chansu, the dried secretion from the skin glands of *Bufo bufo gargarizans* Cantor, has been used clinically as an anti-cancer, anti-inflammatory, analgesic and local anesthetic agent for over a millennium in China. Huachansu, an injectable form of chansu, is an aqueous extract of the dried toad skin. Its primary biologically active chemical components include indole alkaloids, steroidal cardiac glycosides and peptides (Wu et al., 2012). Bufadienolides, a class of cardioactive C-24 steroids with a characteristic α-pyrone ring at C-17, are marker active compounds of Huachansu (Qi et al., 2014). As a widely used natural product in China (approximately 160,000 patients received Huachansu treatments per year), Huachansu has been officially approved by the Chinese Food and Drug Administration as a regimen for treating HBV infection and several cancer including liver, lung, colon, and pancreatic cancer since 1991 (Qi et al., 2014). Both preclinical and clinical studies have demonstrated the anti-cancer properties of Huachansu (Meng et al., 2009; Liu et al., 2015; Qi et al., 2015; Yang et al., 2015). Although Huachansu is not first line therapy for cancer, it is safely used in combination with chemotherapy to promote the therapeutic efficacy and alleviate the side effects (Xie et al., 2013; Wu et al., 2014; Zhou