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DISCOVERY THAT CITRATE, WHICH KEEPS THE BODY'S INTERNAL ENVIRONMENT WEAKLY ALKALINE, IS EFFECTIVE IN PREVENTING OR TREATING PERIPHERAL NEUROPATHY INDUCED BY ANTICANCER DRUGS

Key Points

- Animal studies have shown that keeping the body mildly alkaline is preventive and therapeutic against the mechanical allodynia^{*} induced by the anticancer drug, paclitaxel.
- It is hoped that powerful options can be offered to clinical practice in avoiding the development of chemotherapy-induced peripheral neuropathy (CIPN).

Overview

The research groups of Associate Professor Daisuke Uta of the department of Applied Pharmacology, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, and Dr. Hideki Nakamura of Nippon Chemiphar Co., Ltd. demonstrated in animal experiments that keeping the body's internal environment weakly alkaline inhibited the development of the mechanical allodynia induced by paclitaxel. When citrate, which shows alkalinizing effects in the body, was administered before paclitaxel injection, it prevented the development of mechanical allodynia. It also prevented further severity of CIPN symptoms when citrate was administered from the early stage of mechanical allodynia onset. Alkalinizing effects in the body have therefore shown promise in the prevention and treatment of CIPN.

The results of this study were published online in the International Journal of Molecular Sciences on Thursday, April 3, 2025.

Research background

CIPN is one of the side effects of cancer chemotherapy that occurs after administration of anticancer drugs such as taxanes (paclitaxel, docetaxel), platinum-based drugs (oxaliplatin, cisplatin), vinca alkaloids (vincristine), and proteasome inhibitors (bortezomib). The main symptoms of CIPN are characterized by numbness and pain primarily in the extremities of the hands and feet, which, when severe, can interfere with daily activities. It is consequently considered a clinical challenge not only because it markedly reduces the quality-of-life (QOL) of the patient, but also because it necessitates the reduction or discontinuation of anticancer drugs, which can

affect the prognostication of cancer treatment. However, the detailed mechanisms of CIPN are still unclear, and no effective treatment has been established.

Previous studies have reported that the development of CIPN involves neuroinflammation mediated by immune cells such as microglia, astrocytes, and macrophages, ¹⁻³. Therefore, Associate Professor Uta and Dr. Nakamura and their colleagues focused on the possibility that neuroinflammation may be causing local pH reductions, and examined the effectiveness of in vivo alkalinization for the prevention or treatment of paclitaxel-induced CIPN.

Research content and results

In this study, we fabricated a model of mechanical allodynia by injecting paclitaxel into mice and assessing mechanical allodynia in the hind paw using a filament. As a result, mechanical allodynia onset was confirmed by increased hypersensitivity pain-related responses, such as licking and flinching of the hind paw, compared to control mice.

As shown in Figure 1, the administration of citrate, which is alkalinizing in the body, to CIPN model mice before paclitaxel administration prevented the onset of mechanical allodynia induced by paclitaxel injection. In addition, the administration of citrate at the onset of symptoms prevented further symptoms from becoming more severe.

It is suggested that the mechanisms behind these effects may involve the protective effect of citrate against paclitaxel neurotoxicity and the suppression of complement component activation. As a result, abnormal firing in the spinal dorsal horn nerves may have been suppressed, which may have reduced the development of mechanical allodynia.



Figure 1. Outline of the study results

Future development

The results of this study show that keeping the body's internal environment weakly alkaline has a preventive and therapeutic effect on mechanical allodynia caused by paclitaxel. We hope to demonstrate its efficacy in clinical trials in the future.

Citrate has also been shown to be effective against peripheral neuropathy induced by anticancer drugs other than paclitaxel (oxaliplatin, vincristine, and bortezomib) when applied before administration. Based on the results of these studies, patent applications have also been filed. We believe that continuing further studies can contribute to the improvement of QOL for more people suffering from CIPN.

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[Terminology explanation].

*Mechanical allodynia

Pain caused by tactile stimuli that does not normally elicit pain such as contact, mild compression, friction from clothing, etc.

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[Articles in detail].

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