

TITLE: Slc7a5 (LAT1) inhibition alleviates chemotherapy-induced neuropathic pain

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ABSTRACT:

Background: Chemotherapy-induced neuropathic pain (CINP) is a debilitating and difficult-to-treat side effect of chemotherapeutic drugs. Effective, non-addictive, non-opioid therapeutics are urgently needed for the treatment of chemotherapy associated chronic pain. Slc7a5 (Lat1), also known as system L-neutral amino acid transporter, is involved in a number of physiological processes related to inflammation. Transcriptomics studies have shown that Slc7a5 and its binding partner Slc3a2 are expressed in neurons of the dorsal root ganglia (DRG) and spinal dorsal horn, which are critical to the initiation and maintenance of nociception and pathophysiology of chronic pain. Here, we investigate the role of Slc7a5 in the chemotherapy-induced peripheral neuropathy (CIPN) in rodents mainly using the Slc7a5 blocker, JPH203.

Methods: The mice model of CIPN was established by 5 consecutive intra-peritoneal injections of oxaliplatin (1.0 mg/kg) in every alternative week for five weeks. CIPN mice were treated with either Slc7a5 blocker, JPH203 (12.5 mg/kg), or vehicle, administered intrathecally in a blinded, randomized manner. Pain behavior assessment was made by conducting paw withdrawal mechanical threshold (PWMT) test using von Frey filaments. The effects of JPH203 on nociceptor excitability were measured using whole-cell current clamp electrophysiology of isolated dorsal root ganglion (DRG) neurons.

Conclusions: We found that blocking Slc7a5 with intrathecal administration of the drug JPH203 alleviated oxaliplatin induced mechanical allodynia. Using whole-cell current-clamp electrophysiology, we observed that JPH203 treatment reduced excitability of DRG neurons from chemotherapy-induced peripheral neuropathy (CIPN) mice, in agreement with its behavioral effects. Altogether, these results demonstrate that Slc7a5 is dysregulated in oxaliplatin induced chronic neuropathic pain and can be targeted to provide relief of hypersensitivity.

Keywords: Chronic pain, Chemotherapy-induced peripheral neuropathy (CIPN), Oxaliplatin, Slc7a5 (LAT1), Electrophysiology, Nociceptor

NON-EXPERT SUMMARY

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most frequent adverse events caused by cancer therapeutics like oxaliplatin. Treatment options for oxaliplatin induced CIPN are very limited. The present study is enlightening the role of Slc7a5 (Lat1) in the oxaliplatin-induced peripheral neuropathy in rodents mainly using the Slc7a5 blocker, JPH203. The research findings showed that JPH203 suppressed oxaliplatin-induced mechanical hypersensitivity and neuronal hyperexcitability, therefore, could serve as an attractive drug candidate to mitigate CIPN.