Mechanism of Vincristine-Induced Peripheral Neuropathy.

Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect, manifested by numbness, ticking and allodynia in 30-40% of cancer patients who have taken anticancer drugs chronically. Vincristine is a chemotherapeutic agent with activity against several of the most common cancers, including those of acute lymphocytic leukemia, acute myeloid leukemia, Hodgkin's disease, neuroblastoma and small cell lung cancer. Vincristine exerts its anti-tumor effects by binding to tubulin protein, stopping the cell from separating its chromosomes during metaphase; the cell then undergoes apoptosis. Although CIPN is the most commonly reported neurotoxic and dose-limiting side effect of vincristine, the mechanism of vincristine-induced CIPN remains to be fully defined. Recent observations that CIPN is associated with the development of ectopic spontaneous activity in DRG that itself appears to be related to changes in expression of multiple cell membrane ion channels. Here, we showed that the enhanced expression of the voltage gated sodium channel 1.8 (Nav1.8) of dorsal root ganglia (DRG) via the interaction with interleukin23 (IL23) and its receptor plays an important role in vincristine-induced CIPN. In vincristine-induced CIPN, the increased excitability of DRG neurons was due to the enhanced expression of Nav1.8, not Nav1.7. From microarray of DRG neurons, we confirmed that the interaction with interleukin23 (IL23) and its receptor was strongly associated with vincristine-induced CIPN. In addition, serum IL23 released from the activated dermal dendritic cell was measured 1.51 times higher than in the sham group. In the knockdown experiment of Nav1.8 and IL23R, vincristine-induced CIPN was reduced and inhibition of IL23R downstream, tyrosine kinase 2(TYK2) pathway, with imatinib prevented the induction of vincristine-induced CIPN. Our results reveal that NaV1.8 of DRG neurons plays important roles in vincristine-induced CIPN and the interaction with IL23 and IL23R is responsible for the generation of vincristine-induced CIPN. This study is the first study to clarify the mechanism of vincristine-induced CIPN and suggests a new strategy to prevent CIPN.

Key words.

Chemical induced peripheral neuropathy, Nav1.8, Vincristine, interleukin23, imatinib.