

News Release

Title

An anti-epileptic and anti-Parkinson's disease agent zonisamide enhances neurite elongation of spinal motor neurons

Key Points

- The drug repositioning strategy revealed that zonisamide enhances neurite elongation in mouse primary motor neurons.
- Zonisamide facilitated axonal regeneration, muscle regeneration, and recovery of motor functions in a mouse model of peripheral nerve injury.
- Zonisamide is expected to be effective for peripheral nerve injuries and neuromuscular disorders in clinical settings.

Summary

Professor Kinji Ohno (corresponding author) and Lecturer Bisei Ohkawara at Neurogenetics, and Professor Naoki Ishiguro and a graduate student Hideki Yagi (first author) at Orthopedics in Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, MD, PhD) investigated in collaboration with their colleagues that zonisamide, which is frequently prescribed for epilepsy and Parkinson's disease, enhances neurite elongation of mouse primary motor neurons. They used the drug repositioning strategy, in which a novel application is identified for a drug that is already prescribed for another disease in clinical settings. Zonisamide enhanced regeneration of injured neurites of mouse primary motor neurons. In a mouse model of sciatic nerve autograft, zonisamide facilitated axonal regeneration, muscular regeneration, and induced expression of genes that are specifically expressed at the neuromuscular junction. Zonisamide also increased motor functions. Zonisamide is expected to be effective for treating peripheral neuropathy due to injury and some other causes, as well as for treating neuromuscular disorders in humans. This work was published online in *PLOS ONE* on November 16, 2015.

Research Background

For peripheral neuropathies due to injuries and some other causes, local administrations of the nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), laminins, and cadherin-11 are reported to be effective. Short half-lives and requirement of local administration, however, make the clinical application of these molecules difficult. In a model mouse, cell therapy is also effective, but safety concerns including carcinogenic nature of stem cells must be solved for clinical application. The drug repositioning strategy is for development of a novel application of previously approved medicine. The advantage of the drug repositioning strategy is that the optimal dose, adverse effects, and contraindications are already established, which accelerates cost-effective development of a novel drug without safety concerns. The drug repositioning strategy is especially suitable for orphan

diseases for which pharmaceutical companies cannot invest a large amount of budget to develop a new drug. Zonisamide that we identified in the current studies is already repositioned for Parkinson's disease. Zonisamide was developed originally by Sumitomo Dainippon Pharma Co., Ltd. and released in Japan in 1989 as an anti-epileptic agent. In 2001, the effect of zonisamide on Parkinson's disease was reported. In 2009, zonisamide was approved as a drug for Parkinson's disease and launched by the company.

Research Results

The research team screened a panel of preapproved drugs for neurite elongation of a neuroblastoma and spinal motor neuron hybrid cell line, NSC34, and found zonisamide enhanced neurite elongation and neurite branching in NSC34 cells, as well as in primary mouse spinal motor neurons, in a dose-dependent manner. Neurites of primary spinal motor neurons were allowed to grow on a culture dish and neurites were physically injured. Neurite regeneration was quantitatively traced, and zonisamide enhanced neurite regeneration in a dose-dependent manner (**Fig. 1**). Similarly, when primary motor neurons were cultured under a culture microscope for 80 hours, zonisamide enhanced neurite elongation but had no effect on the initial budding of neurites (**Fig. 2**). Zonisamide induced expressions of neurotrophic factors, *Bdnf*, *Ngf*, and *Ntf4*, and also their receptors, *Ntrk1* and *Ntrk2*. The left sciatic nerve of mouse was cut at two sites with a 3-mm interval and again sutured to make a nerve autograft model. Oral administration of zonisamide increased the axonal areas three-fold at 1 week, improved motor functions at 5 weeks and later, and increased the diameters of muscle fibers at 8 weeks after the surgery. Zonisamide also increased expressions of *Chrne*, *Colq*, and *Rapsn* that are specifically expressed at the neuromuscular junction.

Research Summary and Future Perspective

Zonisamide is a promising drug that can be applied to neuropathies and the subsequent neuromuscular disorders due to injuries and some other causes. Drugs that are available for neuropathies are only vitamins and their derivatives. Zonisamide is a safe drug that has been used for epilepsy in Japan from 26 years ago, in USA from 15 years ago, in EU from 10 years ago. From 6 years ago, zonisamide is used for Parkinson's disease. The effects of zonisamide in human will be scrutinized using human iPS cell-derived spinal motor neurons and neuromuscular junction. Clinical application of zonisamide will also be explored.

Reference

Yagi H, Ohkawara B, Nakashima H, Ito K, Tsushima M, Ishii H, Noto K, Ohta K, Masuda M, Imagama S, Ishiguro N, Ohno K (2015) Zonisamide Enhances Neurite Elongation of Primary Motor Neurons and Facilitates Peripheral Nerve Regeneration In Vitro and in a Mouse Model. *PLOS ONE* 10(11): e0142786.

Japanese ver.

http://www.med.nagoya-u.ac.jp/medical/dbps_data/material/nu_medical/res/topix/2015/zonisamide_20151116jp.pdf

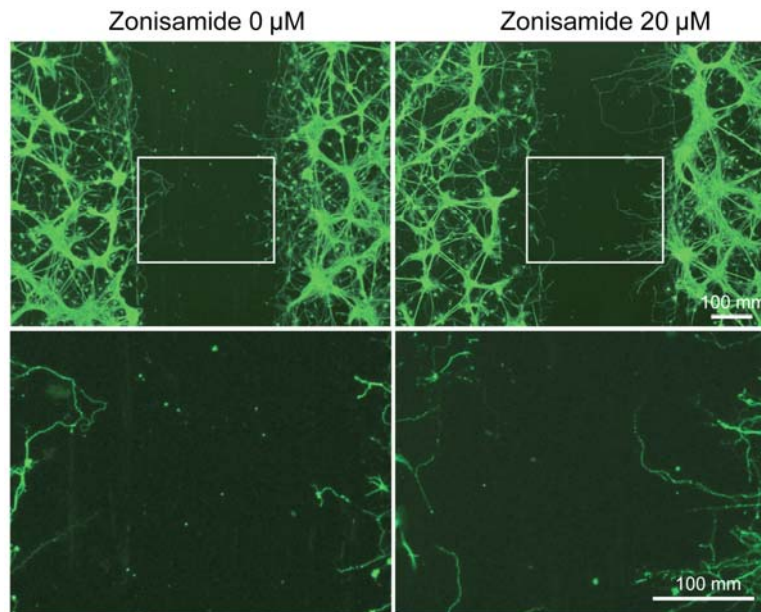


Fig. 1. Neurites of primary spinal motor neurons were allowed to grow on a culture dish and neurites were physically injured (vertical black areas). Automated quantitative analysis of regenerated neurite lengths showed that zonisamide enhanced neurite regeneration. Lower panels are enlarged images of white boxes in the upper panels.

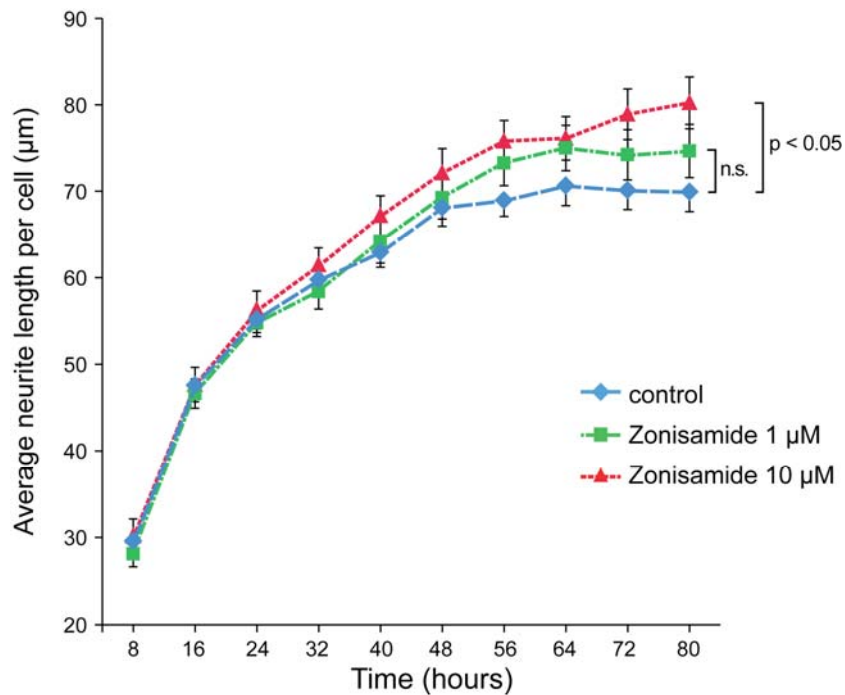


Fig. 2. Mouse primary motor neurons were cultured under a culture microscope for 80 hours. Zonisamide enhanced neurite elongation but had no effect on the initial budding of neurites.