学位の種類	博士（医学）
報告番号	乙第１９２４号
学位記番号	論第１６８０号
氏名	志田 恭子
授与年月日	令和５年 ３月 24 日
学位論文の題名	Peripheral neuropathy in the pre-diabetic state of the type 2 diabetes mouse model (TSOD mice) involves TRPV1 expression in dorsal root ganglions (2 型糖尿病モデルマウス(TSOD マウス)の前糖尿病状態における末梢神経障害の脊髄後根神経節の TRPV1 発現の関与) IBRO Neurosci Rep 2022;12:163-169.
論文審査担当者	主査： 松川 則之 副査： 片岡 洋望, 飛田 秀樹

Abstract

Background: Peripheral neuropathy, which is a complication of diabetes mellitus (DM), is thought to occur in the pre-DM state, being known as impaired glucose tolerance (IGT) neuropathy, although its pathogenesis is unknown. Since it is reversible, an effective treatment at the pre-DM stage could stop the progression of peripheral neuropathy and improve patients' quality of life and reduce medical costs. We investigated the hypersensitivity to mechanical and thermal stimuli during the pre-DM state in Tsumura Suzuki Obese Diabetes (TSOD) mice, a type 2 DM mouse model.

Methods: The pre-diabetic state of TSOD and Tsumura Suzuki Non-Obesity (TSNO) mice were confirmed from measurements of body weight, blood glucose, urinary glucose, and insulin tolerance test. Mechanical allodynia was evaluated with von Frey filaments and thermal hypersensitivity with a hot plate device. Immunohistochemistry was used to analyze the diameter distribution of Transient Receptor Potential Vanilloid 1 (TRPV1)-positive cells in the dorsal root ganglia (DRG) of 12-week-old TSOD and TSNO mice. Additionally, immunofluorescent double staining for TRPV1 and NF-H (neurofilament heavy) was performed in the DRG.

Result: The expression pattern of the TRPV1-positive cells in the DRG was examined in TSOD mice, which showed a pre-DM state at 5–12 weeks of age and decreased mechanical and thermal nociceptive thresholds. Additionally, the size of TRPV1-positive cells in TSOD mice increased compared with that in non-diabetic controls (TSNO mice). Furthermore, the expression of TRPV1 on myelinated nerve fibers (NF-H-positive cells) had significantly increased.

Conclusion: TSOD mice in the pre-DM state at 5–12 weeks of age could be a useful animal model of IGT neuropathy. We also hypothesized that the development of IGT neuropathy may involve a switch in TRPV1 expression from small, unmyelinated neurons to large, myelinated neurons in the DRG.