1. **No.**

   FP01907130

2. **Title**

   Investigation of Utility of Nicotine and Its Derivatives as Novel Therapeutic Drugs for Chemotherapy-induced Peripheral Neuropathy

3. **Period**

   2016-2020

4. **Summary**

Paclitaxel, a microtubule stabilizer, frequently causes the chemotherapy-induced peripheral neuropathy (CIPN). The present study was designed to investigate the utility of nicotinic acetylcholine receptor (nAChR) and muscarinic acetylcholine receptor (mAChR) agonists as novel therapeutic drugs for CIPN. We found that the mRNA expression of muscarinic M1-M5 receptors or α3, α7 and β4 nicotinic receptors in differentiated primary cultured Schwann cells obtained from the sciatic nerves of Wistar/ST rat pups. Among screened 11 nAChR and mAChR agonists, we selected an α7nAChR agonist, GTS-21, which has the ability to induce Schwann cell differentiation, as a candidate for a therapeutic drug for CIPN. GTS-21 inhibited paclitaxel-induced Schwann cell dedifferentiation accompanied with up-regulation of an inflammatory factor, and demyelination in the Schwann cell/dorsal root ganglia (DRG) neuron co-cultures. Furthermore, mechanical hypersensitivity induced by paclitaxel was significantly suppressed by GTS-21 injection at 7 days after the paclitaxel injections. GTS-21 almost completely inhibited the elevation of the plasma level of the inflammatory factor and infiltration of Iba1-labeled macrophages into the sciatic nerves in paclitaxel-injected mice. These effects induced by GTS-21 were canceled by the co-treatment of an α7nAChR antagonist, methyllycaconitine. In conclusion, we propose here that GTS-21, which has the ability to prevent paclitaxel-induced dedifferentiation or promote Schwann cell redifferentiation and remyelination, may be a novel strategy for treating CIPN. These effects by GTS-21 seem to be mediated by the agonism for α7nAChR.