WLS-1, a Natural Marine Compound, Attenuates Nociception And Spinal Neuroinflammation in Streptozotocin-Induced Diabetic Rats

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Diabetes mellitus is a metabolic disease that can have long-term complications, including diabetic peripheral neuropathy (DPN). We had found, through preliminary screening, that WLS-1, a natural marine compound isolated from corals, has potential *in vitro* anti-inflammatory effects. In the present study, we investigated the antinociceptive effects on intrathecal (i.t.) and oral administration of WLS-1 in streptozotocin (STZ)-induced diabetic neuropathic rats. First, we observed that a single i.t. administration of WLS-1 results in dose-dependent antinociceptive effects in diabetic rats. Moreover, ziconotide, a positive control, caused serious side effects at analgesic doses in diabetic rats, whereas WLS-1 did not. Immunohistochemistry analyses showed that i.t. WLS-1 significantly attenuated STZ-induced activation of microglia and astrocytes, as well as the upregulation of inflammatory mediator interleukin-1 (IL-1), on the lumbar superficial dorsal horn. In addition, we observed the upregulation of the anti-inflammatory cytokine transforming growth factor- 1 (TGF- 1) in the lumbar superficial dorsal horn of diabetic rats after i.t. administration of WLS-1. Next, we utilized oral administration of WLS-1 to further characterize its systemic effect on neuropathic pain in diabetic rats. We found that oral administration of WLS-1 and gabapentin had antinociceptive effects on STZ-induced pain behaviors, without changes in blood sugar levels. The activation of spinal microglia and astrocytes, as well as the upregulation of IL-1 . in STZ-rats were significantly suppressed by oral WLS-1. In conclusion, we have demonstrated the antinociceptive ability of central and systemic WLS-1, which is probably due to its anti-neuroinflammatory effects. Therefore, our findings indicate that WLS-1 is a potential candidate compound for drug development to treat neuropathic pain in patients with diabetes.