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Therapeutic Efficacy of NSI-189 against Diabetic Neuropathy and Encephalopathy in Mice

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NSI-189 is a novel orally active neurogenic small molecule that penetrates the CNS and stimulates neurogenesis, synaptogenesis and increased hippocampal volume in mice. NSI-189 is currently in a Phase 2 clinical trial for major depressive disorder. The neurotrophic and neuroprotective properties of NSI-189 promoted us to determine efficacy of NSI-189 against indices of neuropathy and encephalopathy in a mouse model of type 1 diabetes. Swiss Webster mice with streptozotocin-induced diabetes (90 mg/kg ip, 2 consecutive days) were treated with insulin (sub-cutaneous pellet) or NSI-189 (10mg/kg/day by gavage) from onset of diabetes for 8 weeks. Nerve function and structure was assessed at regular intervals throughout the study. At study end, insulin had normalized blood glucose and HbA1c levels in diabetic mice and prevented motor nerve conduction slowing, tactile allodynia, paw thermal hypoalgesia, depletion of epidermal and dermal fibers, depletion of corneal stromal and sub-basal nerve plexus fibers and impaired Barnes maze performance. NSI-189 was without discernable effect on general physiology or nerve function in control mice and did not alter the severity of systemic diabetes. NSI-189 given from onset of diabetes significantly ($P<0.05$) improved all indices of peripheral nerve function and structure compared to vehicle-treated diabetic mice. It also significantly ($P<0.05$) prevented loss of long-term memory in the Barnes maze test. Quantification of neuronal volume in the CA1, CA3 and dentate gyrus regions of the hippocampus revealed a significant ($P<0.05$) loss of volume in diabetic mice compared to control mice that was prevented or attenuated by insulin. NSI-189 also significantly ($P<0.05$) attenuated loss of volume in the CA1 and dentate gyrus. As NSI-189 is currently in clinical trial for major depressive disorder, the rapid translation of this therapy for clinical investigation against diabetic neuropathy and encephalopathy is possible.