# Differential time course of glycogen synthase kinase-3 inhibition in experimental autoimmune encephalomyelitis


## ABSTRACT

Introduction: GSK-3 is an immune regulator that plays a role in the modulation of cytokine-producing effector T cells associated with inflammation and demyelination of the CNS in EAE. Objective: This study aimed to evaluate the treatment paradigm of a single dose of GSK-3 inhibitor administration at various time courses for the protection of the CNS from EAE. Materials and methods: Effects of GSK-3 inhibition on intracellular cytokine levels were evaluated from in vitro naïve CD4+ T cell cultures. Immunized C57BL/6 female mice with MOG35-55 in conjunction with CFA and Ptx were used as a chronic inflammatory EAE disease model. Tideglusib (NP12), a Thiadiazolidinone class, selective, and non-ATP competitive GSK-3 inhibitor, was injected intraperitoneally at pre-EAE, same-day of immunization or disease onset. After 30 days post-immunization, brain, and spinal cord tissues were collected for inflammation and demyelination analysis by H&E and luxol fast blue staining, respectively, whereas cytokine profiles of the serum were assessed by cytokine beads array. Results: The inhibition of GSK-3 in CD4+ T cells increased IL-10 production. The administration of Tideglusib during pre-EAE and same-day, but not during disease onset, significantly reduced clinical symptoms and delayed disease onset. Histopathological analysis of spinal cord tissues showed a significant decline in the number of inflammatory cell infiltration with a concomitant reduction in demyelination through the blocking of GSK-3, especially during pre-EAE and sameday. Upregulation of IL-10 via GSK-3 inhibition coincided with the downregulation of cytokineassociated effector T cells, including IFN-γ, IL-9, IL-17A, IL-17F, IL-21, and IL-23. Increased IL-4 production, however, was only significant in the pre-EAE group. Conclusion: The neuroprotective effects of Tideglusib against EAE are time-dependent. Downregulation of Th1 and Th17 hallmark cytokines by Tideglusib in EAE may be associated with IL-10 production.



**Keyword:** Glycogen synthase kinase-3; Multiple sclerosis; Experimental autoimmune encephalomyelitis; Central nervous system; Neuroinflammation; Interleukin-10 (IL-10)