Regulation of MEF2 by a small molecule modulates neuronal synapses

N Jayathilaka\(^1,2\), V Balasanyan\(^1\) and L Chen\(^1\)

\(^1\)Molecular and Computational Biology, Department of Biological Sciences, University of Southern California, Los Angeles, CA 90089
\(^2\)Department of Chemistry, University of Kelaniya, Kelaniya, Sri Lanka

Epigenetic modifications and their effect on complex neuronal processes like learning and memory have attracted much attention in therapeutic development for neurodegenerative disorders. Histone acetylation, regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), is one such modification critically involved in gene regulation in neurons. The myocyte enhancer factor-2 (MEF2) is a family of transcription factors that are highly expressed in the brain. These factors are regulated by signal dependent recruitment of transcription co-repressors such as HDACs or co-activators such as CBP/p300. MEF2 dependent transcription has been shown to regulate synapse formation while HDAC inhibitors have been shown to increase histone acetylation and synaptic plasticity in neurons and enhance memory. Therefore, targeting the interaction between MEF2 and HDACs presents a potential approach to regulate synapses and memory.

In this study a small molecule, termed NKL-30 that regulates the transcription function of MEF2 by blocking its interaction with class IIa HDACs without affecting the MEF2/ P300 interaction is described. Treatment of rat cortical neurons with NKL-30 led to a significant decrease of excitatory synapse number, which is similar to that seen when MEF2-dependent transcription was activated in hippocampal neurons and cerebellar granule cells. Our studies link MEF2-dependent genetic programs and synaptic morphogenesis to the effects of histone deacetylase inhibitors on learning and memory. In fact, these findings present a possible mechanism for HDAC inhibitor mediated specific gene expression and memory enhancement. The small molecule established here provides a tool for further studying the molecular mechanisms of memory and for drug development against neurological diseases.

Keywords: Epigenetic regulation, HDAC inhibitors, neurological disorders, synaptic plasticity

njayathi@gmail.com

Tel: 0772069887