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A complex-selective and safe HDAC inhibitor with pro-synaptic effects - A promising therapy for neurodegenerative disorders

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Abstract

Post-translational modifications of histone proteins, such as acetylation, play a central role in regulating neuronal gene expression and brain function. Emerging evidence implicates dysregulation of gene expression in cognitive and neurodegenerative disorders. Previous studies have shown that increase in histone acetylation enhances synaptic plasticity, learning and memory. Therefore, treatment with histone deacetylases inhibitors (HDACi) is a promising strategy for therapeutic intervention in neurological disorders with synaptic pathology. However, the combination of limited brain penetration and lack of specificity of HDACis has led to peripheral side effects and limited viability for any chronic human therapy. Here, Rodin Therapeutics describes proprietary compound Rodin-A, a brain penetrant, safe, and selective inhibitor of HDAC1 and HDAC2. Chronic treatment *in vivo* with Rodin-A significantly increased (27%) spine density in the CA1 region of the dorsal hippocampus of wild type mice and improved the impaired LTP in the 5xFAD mice, a model of Alzheimer disease (AD). Furthermore, Rodin-A treatment resulted in increased levels of pre- and post-synaptic proteins and phosphorylated tropomyosin-related kinase B receptor (pTrkB), a neurotrophin receptor known to promote LTP and synaptic plasticity. While previously studied HDACi, such as CI-994, showed pro-synaptic effects *in vivo*, lack of therapeutic window precluded use to treat neurological disorders. Rodin-A achieves equivalent pro-synaptic effects with a substantially improved safety margin. Together, our results describe a new, selective and safe HDACi which modulates structural and synaptic plasticity. Rodin-A represents a new potential therapeutic intervention in disorders of synaptic plasticity and cognition, including neurodegenerative disorders such as AD.