The small molecule class IIa HDAC inhibitor TMP269 protects against degeneration in *in vitro* models of Parkinson's Disease

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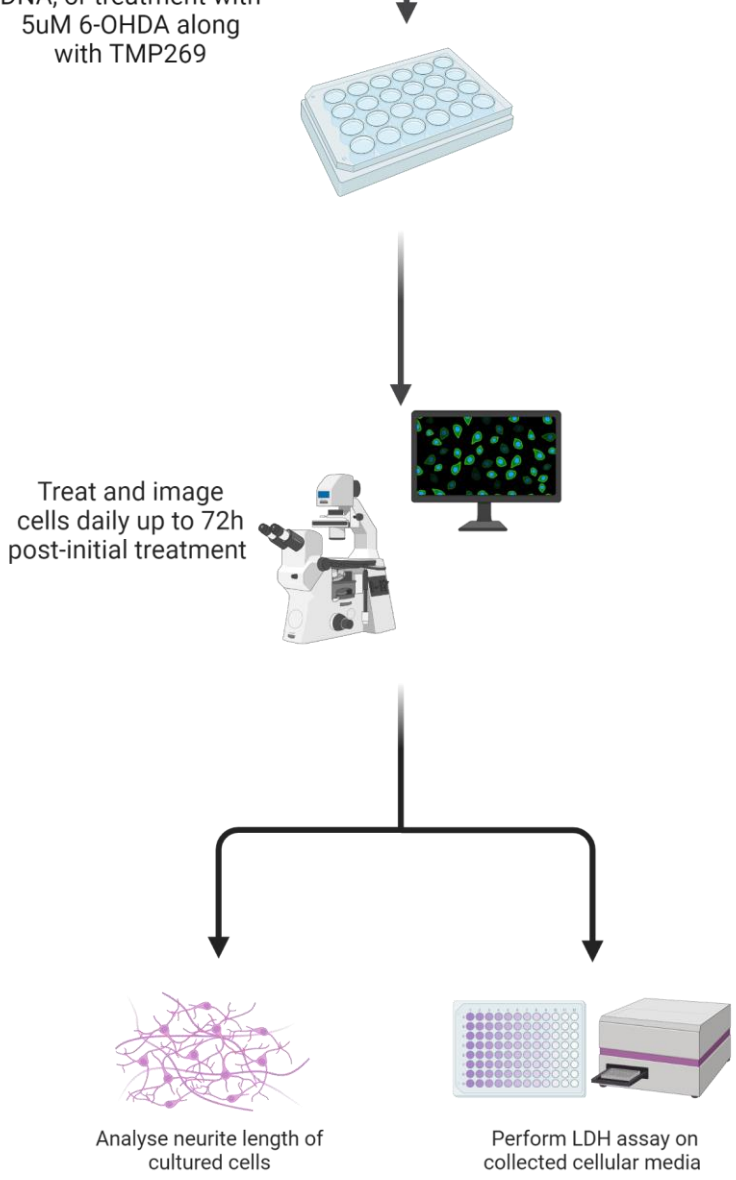
Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease globally, characterized by midbrain dopaminergic (mDA) neuronal degeneration, leading to progressive motor impairments. The main pathological hallmark of PD is accumulation of the protein α-synuclein into insoluble aggregates known as Lewy bodies and Lewy neurites. There is no disease modifying therapy for PD, thus identification of new therapies that protect and/or regenerate dopaminergic neurons is essential. Epigenetic modifications, specifically alterations in histone acetylation levels, are associated with the progression of PD pathology. Higher levels of histone acetylation have been reported in mDA neurons of PD patients, when compared to control groups [1]. This has led to consideration of histone deacetylase (HDAC) inhibitors as potential disease modifying therapies targeting histone acetylation. Previous studies by our group have identified the class-IIa HDAC family as targets of interest, reporting neuroprotective effects of specific class-IIa inhibitors on mDA neurons; furthermore, gene co-expression analysis identified the presence of the class-IIa HDACs, HDAC5 and HDAC9, in mDA neurons, making them promising therapeutic targets [2][3].

Objectives

To assess the therapeutic efficacy of the pharmacological class IIa HDAC inhibitor TMP269 in protecting against degeneration *in vitro* caused by the dopaminergic neurotoxin 6-Hydroxydopamine (6-OHDA) or α-synuclein-induced neurite injury

Methods

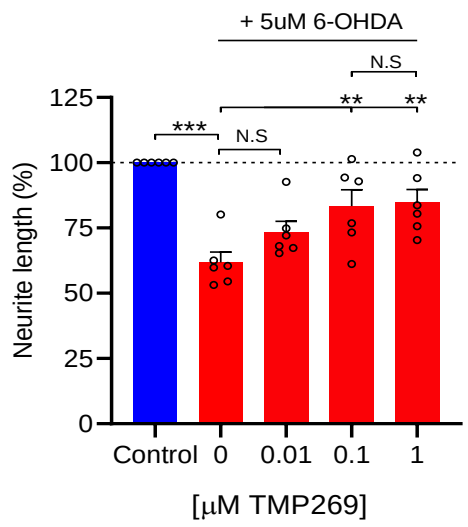


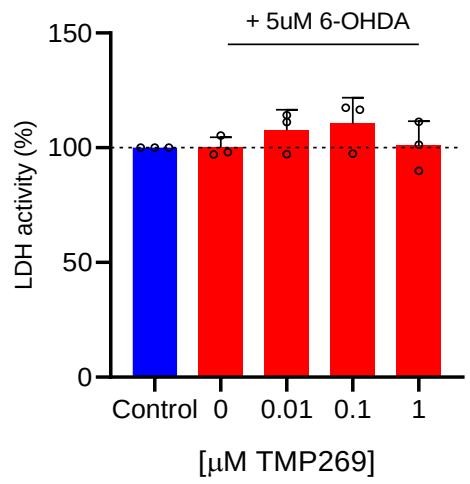
Conclusion

Pharmacological class IIa HDAC inhibition by TMP269 is protective against both 6-OHDA and α-synuclein-induced neurite injury

Results

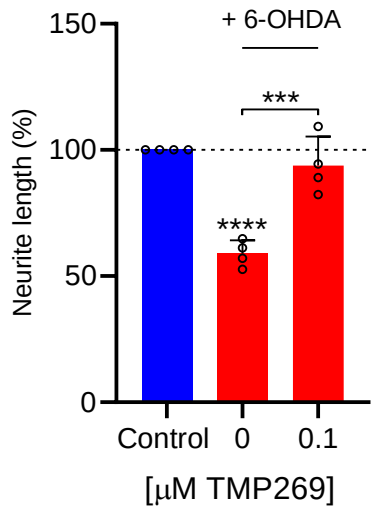
TMP 269 Treatment results in significant increase in neurite length in 6-OHDA-induced degeneration

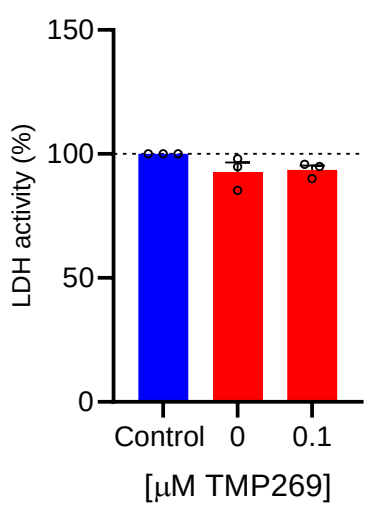




Data represented as mean +/- SEM as a percentage of the untreated group from *n* = 6 independent experiments. , (**p<0.01, ***p<0.0001, versus untreated control, or as indicated), one-way ANOVA with *post-hoc* Tukeys's test

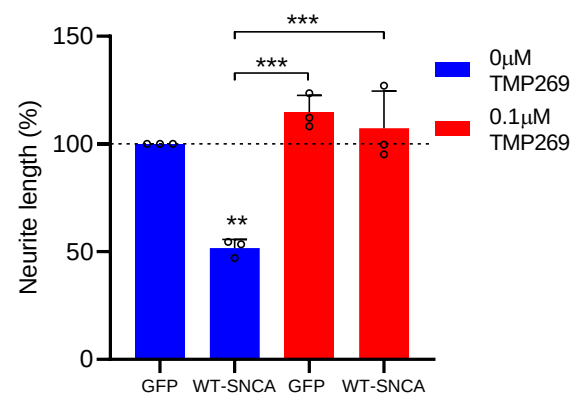
Delayed TMP269 treatment results in significant increase in neurite length following 6-OHDA-induced degeneration

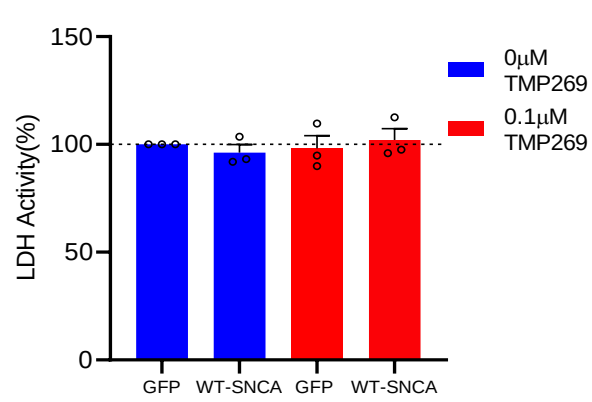




Data represented as mean +/- SEM as a percentage of the untreated group from *n* = 3 independent experiments. , (***p<0.001, ****p<0.0001, versus untreated control, or as indicated) one-way ANOVA with *post-hoc* Tukey's test

TMP269 Protects against α-synuclein induced neurite degeneration





Data are presented as mean +/- SEM as a percentage of the untreated group from *n* = 3 independent experiments, (**p<0.01, ***p<0.001 versus GFP control group, or as indicated) one-way ANOVA with *post-hoc* Tukeys's test

References & Affiliations

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[3] Mazzocchi M, Wyatt SL, Mercatelli D, Morari M, Morales-Prieto N, Collins LM, Sullivan AM and O'Keeffe GW (2019) Gene Co-expression Analysis Identifies Histone Deacetylase 5 and 9 Expression in Midbrain Dopamine Neurons and as Regulators of Neurite Growth via Bone Morphogenetic Protein Signaling. Front. Cell Dev. Biol.

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