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SAHA is neuroprotective in in vitro and in situ models of retinitis pigmentosa.

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PURPOSE: Recent reports linking HDAC6 to mitochondrial turnover and neurodegeneration led us to hypothesize that an inhibitor such as Vorinostat (suberoylanilide hydroxamic acid, SAHA) may reduce mitochondrial damage found in retinitis pigmentosa (RP), a progressive neurodegenerative disease of the eye. Here we tested the efficacy of SAHA for its ability to protect photoreceptors in in-vitro and in-situ models of RP. As the stressor, we focused on calcium overload. Calcium is one of the main drivers of cell death, and is associated with rod loss in the rd1 mouse retina, which harbors a mutation in the Pde6b gene similar to that found in human patients suffering from autosomal recessive RP. METHOD: Murine photoreceptor cell line (661W) were exposed to agents that led to calcium stress. Cell survival and redox capacity were measured using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, real-time changes in cellular metabolism were assessed using the Seahorse Biosciences XF24 analyzer, and mitochondrial fission-fusion using imaging. In-situ, neuroprotection was assessed in RPE/retina organ cultures of the rd1 mouse. SAHA effects on cell survival were compared in 661W cells with those of the specific HDAC6 inhibitor tubastatin A, and those on protein acetylation by Western blotting. RESULTS: In stressed 661W cells, SAHA was found to increase cell survival that was associated with improved mitochondrial respiration and reduced mitochondrial fission. The protective effects of SAHA were also observed on photoreceptor cell survival in whole retinal organ explants of the rd1 mouse. Even though tubastatin A was ineffective in increasing cell survival in 661W cells, HDAC6 activity was confirmed in 661W cells after SAHA treatment with protein acetylation specific for HDAC6, defined by an increase in tubulin, but not histone acetylation. CONCLUSIONS: SAHA was found to protect mitochondria from damage, and concomitantly reduced photoreceptor cell death in cell and organ cultures. The lack of activity of tubastatin A suggests that there must be an additional mechanism of action involved in the protective mechanism of SAHA that is responsible for its neuroprotection. Overall, SAHA may be a useful treatment for the prevention of photoreceptor degeneration associated with human RP. The results are discussed in the context of the effects of inhibitors that target different classes and members of the HDAC family and their effects on rod versus cone survival.

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