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Impact of inhibitors of histone deacetylases on survival and intracellular stress responses of neuroblastoma SH-SY5Y cells

Juraj Michalička [1], Monika Lišková [1], Jaroslava Gužíková [1], Peter Račay [1]

[1] Department of Medical Biochemistry, Comenius University in Bratislava, Jessenius Faculty of Medicine in Martin, Slovakia.

Correspondence to: Prof. Peter Račay PhD, Department of Medical Biochemistry, Jessenius Faculty of Medicine, Comenius University, Malá Hora 4D, SK-03601 Martin, Slovak Republic.
TEL: +421-43-2633443, E-MAIL: peter.racay@uniba.sk, ORCID: 0000-0003-2166-1556

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Abstract

OBJECTIVES: Histone deacetylases (SHDAC) are enzymes that catalyse removal of acetyl group from lysine side chains of histones and non-histone proteins. Inhibitors of HDAC (HDACi) are extensively studied because of their ability to induce death of tumour cells. HDACi are also studied as neuroprotective molecules in different models of neurodegenerative diseases. We have examined impact of HDACi, butyrate and vorinostat, on relative survival of SH-SY5Y cells and intracellular stress response.
METHODS: Relative cell survival was determined by MTT assay and light microscopy. The expression of the key stress proteins was determined by Western blot analysis.
RESULTS: We have shown that both butyrate and vorinostat have significant negative impact on relative survival of SH-SY5Y cells. Treatment of the cells with vorinostat was associated with significantly increased expression of HRD1 that is protein of ER stress response. Expression of HRD1 was also elevated in the cells treated with butyrate but the increase was not statistically significant. Both butyrate and vorinostat did not significantly affect expression of mitochondrial HSP60 as a protein of mitochondrial stress and HSP70 that is upregulated after proteasome stress.
CONCLUSION: Negative impact of vorinostat on survival of neuronal cells could account for neuropathy observed as an adverse effect of the treatment of cutaneous T-cell lymphoma with vorinostat. The potential of HDACi including vorinostat to induce ER stress proteins is probably not associated with neuproprotective effects of HDACi.

Introduction

Histone deacetylases (HDAC) are enzymes that catalyse removal of acetyl group from lysine side chains of histones and non-histone proteins. Different types of HDAC that are coded by 18 genes were subdivided into two groups by their dependency on Zn^{2+} and four classes by their homology to yeast proteins, resulting in Zn^{2+}-dependent enzymes including class I, II and IV and Zn^{2+}-independent enzymes of class III HDAC that require NAD^+ for their activities (Shvedunova & Akhtar 2022). Inhibitors of HDAC (HDACi) are changing the steady state of the cells towards increased acetylation of proteins. Acetylation of histones represents important posttranslational modification of histones that is associated with chromatin relaxation and increased accessibility of transcription factors to the *cis*-regulatory elements of DNA resulting in transcription of specific genes (Shvedunova & Akhtar 2022). In addition to the changes in gene expression, alterations of protein acetylation can induce changes in cell signalling independent of transcription (Shvedunova & Akhtar 2022). HDACi are extensively studied because of their ability to induce death of tumour cells (Falkenberg & Johnstone 2014; Mabe *et al.* 2024) including neuroblastoma (Phimmachanh *et al.* 2020; Qiu & Matthay 2022) and glioblastoma cells (Chen *et al.* 2020). In contrast, HDACi are also studied as potent neuroprotective molecules (Falkenberg & Johnstone 2014; Shukla & Tekwani 2020; Park *et al.* 2025) since hypoacetylation can be associated with neurodegeneration and memory loss (Selvi *et al.* 2010; Park *et al.* 2025). The mechanisms of neurodegeneration caused by alterations of protein acetylation include changes in both gene expression and cell signalling resulting in deregulation of neuronal physiological homeostasis resulting in neuronal cell dysfunction or death (Park *et al.* 2025). Alterations of protein acetylation can also result in accumulation of pathophysiological proteins such as tau, α-synuclein, and Huntingtin protein implicated in pathophysiology of Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), respectively (Kabir *et al.* 2023). In amyotrophic lateral sclerosis (ALS), dysregulation of acetylation is also linked to impaired axonal transport as a key pathological mechanism of ALS (Kabir *et al.* 2023).

In this study, we have examined impact of HDACi, butyrate and vorinostat, on relative cell survival and intracellular stress response. Butyrate is short chain fatty acid that is produced by fermentation of colonic bacteria (Mann *et al.* 2024) and that is primarily metabolized by colonocytes as an energy source (Donohoe *et al.* 2011; Park *et al.* 2025). A fraction of butyrate is metabolised in the liver by β-oxidation (Pant *et al.* 2023). Butyrate is an inhibitor of HDAC Class I and Class IIa (Park *et al.* 2025). Vorinostat is an inhibitor of HDAC Class I, Class IIa and Class IIb (Park *et al.* 2024a) that was approved by FDA for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (Duvic & Vu 2007). Vorinostat is the first HDACi entering the trial for patients with glioma (NCT00238303). Since both dysfunction of ubiquitin-proteasomal system (Thibaudeau *et al.* 2018; Davidson & Pickering 2023) and mitochondria (Bustamante-Barrientos *et al.* 2023; Klemmensen *et al.* 2024) as well as stress of endoplasmic reticulum (ER) (Hetz & Saxena 2017; Singh *et al.* 2024) are often implicated in the mechanisms of neurodegenerative diseases we have investigated impact of butyrate and vorinostat on the expression of the proteins of intracellular stress responses. We have focused our interest on HRD1 that is E3 ubiquitin ligase induced in response to ER stress (Dibdiakova *et al.* 2019). We have also determined expression of HSP70 that is key protein induced by proteasomal stress (Bush *et al.* 1997; Pilchova *et al.* 2017) and HSP60 that is induced by mitochondrial stress (Fiorese *et al.* 2016). We have performed our study on SH-SY5Y cells that are used as a cell model to study molecules that could be employed for the treatment of neuroblastoma (Geng *et al.* 2016; Bayat Mokhtari *et al.* 2017; Kaneda *et al.* 2022). In addition, SH-SY5Y cells that can be differentiated to dopaminergic neurons are widely used in neurobiology to study dopaminergic neurodegeneration in the cellular models of PD (Alrashidi *et al.* 2021; Evinova *et al.* 2024).

Material and methods

Sodium butyrate, (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), sodium dodecylsulphate (SDS) (all from Sigma Aldrich). Vorinostat (MedChemExpress). Mouse monoclonal antibodies against GAPDH (SC-166574, Santa Cruz Biotechnology), HSP70 (SC-13132, Santa Cruz Biotechnology) and HSP60 (SC-271215, Santa Cruz Biotechnology); rabbit polyclonal antibody against HRD1 (13473-1-AP, Proteintech); goat anti-rabbit (A0545, Sigma-Aldrich) and goat anti-mouse (A0168, Sigma-Aldrich) secondary antibodies conjugated with horse radish peroxidase.

Culturing, treating and harvesting of SH-SY5Y cells

Undifferentiated human neuroblastoma SH-SY5Y cells (ATCC) were cultured at 37 °C, 5% CO2 humidified atmosphere maintained in medium DMEM:F12 (1:1) (Dulbecco's Modified Eagle's Medium and Ham's *F-12* Nutrient Mixture, Sigma) supplemented with 10% FBS and 1% penicillin streptomycin stock (all PAA). The medium was changed every 2–3 day until achieving the 80% confluence.

SH-SY5Y cells were treated with either butyrate at a concentration 2 mmol/L or vorinostat at a concentration 5 μmol/L for 24 h at 37 °C under a 5% CO_2 humidified atmosphere. At the end of the treatment, the cells were washed 3 times with ice-cold phosphate-buffered saline (PBS) and then re-suspended in a lysis buffer (30 mM Tris-HCl, 150 mM NaCl, 1% CHAPS,

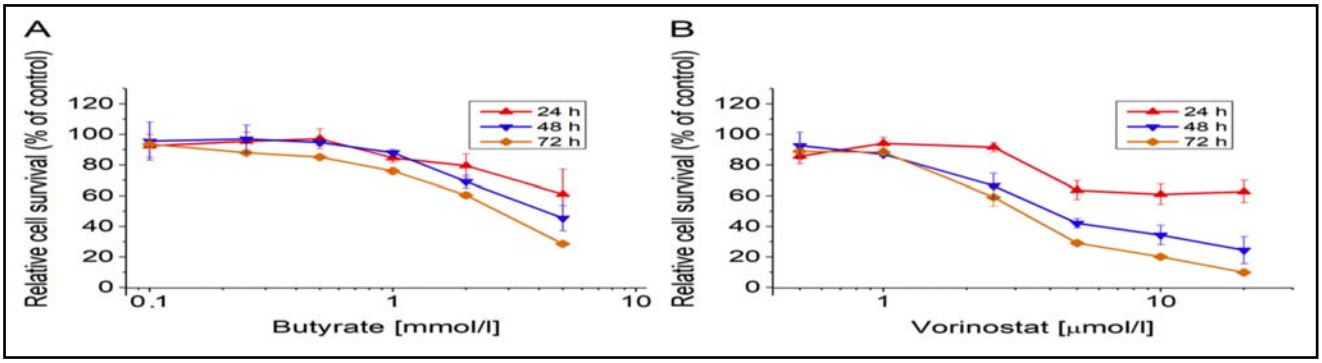

Fig. 1. The effect of butyrate (A) and vorinostat (B) on relative viability of SH-SY5Y cells
SH-SY5Y cells were incubated with indicated concentrations of either butyrate or vorinostat for 24, 48, and 72 h and then the relative cell viability was determined by MTT test as described in Material and Methods. Data are presented as means ± SD.

1x protease inhibitor cocktail, pH = 7.6) for total protein extraction. Protein concentrations were determined by a protein DC assay kit (Bio-Rad) with BSA as a standard.

Cell viability

The cells were seeded in 96-well plates at optimal concentrations. Control cells and the cells treated with indicated concentrations HDACi were incubated for 24, 48 and 72 h at 37 °C under a 5% CO_2 humidified atmosphere. At the end of incubation, a 0.01 mL MTT solution (5 mg/mL) was added to each well, and the cells were further incubated for 4 hours at 37 °C and under a 5% CO_2 humidified atmosphere. The insoluble formazan, which resulted from the oxidation of added MTT by vital cells, was dissolved by the addition of 0.1 mL of SDS solution (0.1 g/mL) and overnight incubation at 37 °C under a 5% CO_2 humidified atmosphere. The absorbance of formazan was determined spectrophotometrically by using a Synergy H4 microplate reader (Agilent). The relative viability of the cells was determined as the ratio of the optical density of formazan produced by treated cells to the optical density of the formazan produced by untreated control cells and was expressed as a per cent of the control. For each treatment time, the optical density value of untreated control cells was considered as 100% of viable cells.

Western blotting

Isolated proteins (30 μg proteins loaded per lane) were separated on 10% SDS-polyacrylamide gel electrophoresis (PAGE) under reducing conditions. Separated proteins were transferred to nitrocellulose membranes by using semi-dry transfer, and membranes were probed with antibodies specific to HSP70 (1:1000), HRD1 (1:1000), HSP60 (1:1000) and GAPDH (1:2000). Further incubation of the membranes with particular secondary antibodies (1:10 000 mouse, 1:20 000 rabbit) was followed by the visualization of immunopositive bands by using the chemiluminiscent substrate Super-Signal West Pico (Thermo Fisher Scientific) and the Chemidoc XRS system (Bio-Rad). Intensities of specific bands were quantified by Quantity One software (Bio-Rad). The intensities of bands of interest were normalized to corresponding intensities of bands of β-actin and were expressed as the intensity of the band of the particular protein in treated cells relative to the intensity of the band in control untreated cells.

Results

The treatment of the cells with different concentrations of either butyrate or vorinostat for 24, 48 and 72 h was associated with concentration-dependent reduction of the relative viability of SH-SY5Y cells (Fig. 1). The cell death induced by butyrate was relative fast while the death of the cells treated with vorinostat was more prominent after 48h of treatment.

The death of the cells was confirmed using light microscopy. As shown on Fig. 2, treatment of the cells with either butyrate at a concentration 5 mmol/L or vorinostat at a concentration 20 μmol/L for 48 h was associated with disappearance of the cells exhibiting normal morphology as seen in control untreated cells. Instead of this, circle shaped bodies were observed indicating cellular disintegration and cell death. Especially cells treated with vorinostat were turned to the bodies with a shape consistent with morphology of apoptotic cell bodies and apoptotic vesicles.

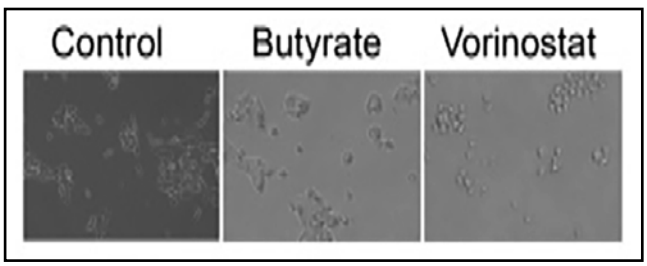

Fig. 2. The effect of butyrate and vorinostat on morphology of SH-SY5Y cells
Phase contrast microscopy images were made after the incubation of SH-SY5Y cells with either butyrate (5 mmol/L) or vorinostat (20 μmol/L) for 48 h.

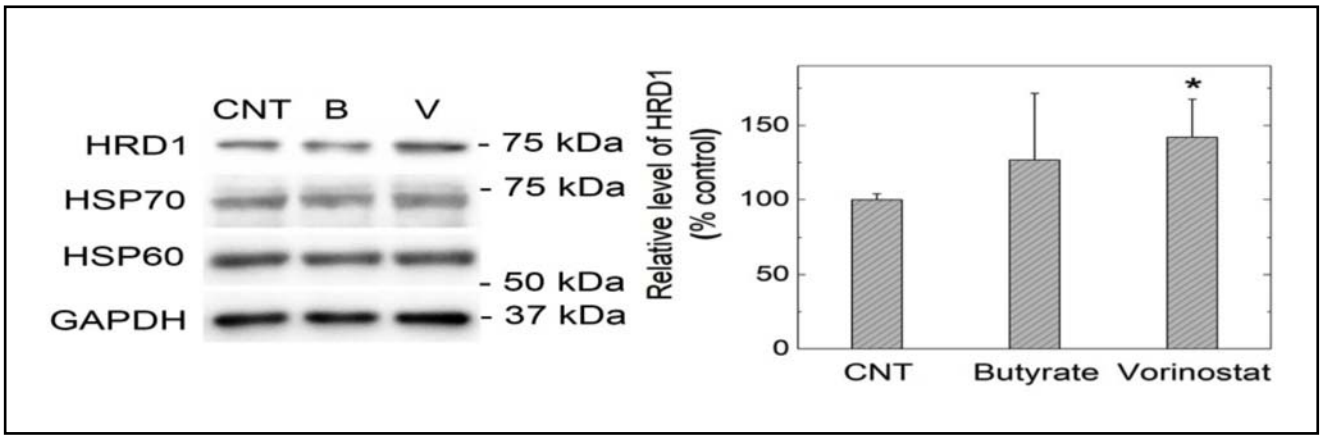

Fig. 3. Effect of butyrate (B) and vorinostat (V) on the level of HRD1, HSP70 and HSP60

Total cell extracts were prepared from control untreated cells (CNT) and the cells treated with either butyrate (2 mmol/L) and vorinostat (5 μmol/L) for 24 h. The impact of HDACi on the levels of HRD1, HSP70 and HSP60 was evaluated by Western blot analysis of total cell extracts as described in Materials and Methods.

Quantification of the levels of HRD1 in SH-SY5Y was performed after exposition of the membranes on Chemidoc XRS (Bio-Rad). The intensities of the corresponding bands were determined using Quantity One software (Bio-Rad). The data were normalised to GAPDH level and expressed as intensity of band of HRD1 protein relative to intensity of the band of GAPDH. Data are presented as means ± SD (3 independent experiments per each HDACi). *$p < 0.05$ (ANOVA, followed by Tukey's test to determine the differences between levels of HRD1 in control untreated cells and cells treated with particular HDACi).

In order to test the impact of HDACi on expression of proteins involved in the cellular responses to mitochondrial, proteasome and ER stress we have performed Western blot analysis of the protein extracts prepared from control untreated cells and the cells treated with indicated concentrations of either butyrate or vorinostat for 24h. We have focused our interest on HRD1 that is E3 ligase involved in ER stress (Dibdiakova *et al.* 2019), HSP70 that is key protein induced by proteasomal stress (Bush *et al.* 1997; Pilchova *et al.* 2017) and HSP60 that is induced by mitochondrial stress (Fiorese *et al.* 2016). As shown on Fig. 3, treatment of SH-SY5Y cells with vorinostat at a concentration 5 μmol/L for 24 h was associated with statistically significant increase of HRD1 level (142% of control, $p < 0.05$). The level of HRD1 was also elevated in the cells treated with butyrate at a concentration 2 mmol/L (142% of control) but the change was not statistically significant.

Discussion

In this study, we have documented the sensitivity of SH-SY5Y cells to HDACi, butyrate and vorinostat. While butyrate induces cell death at millimolar concentrations, vorinostat is potent to induce cell death at micromolar concentrations. In addition, we have shown induced expression of ER stress protein HRD1 after incubation of SH-SY5Y cells with vorinostat.

Sensitivity of SH-SY5Y cells to butyrate is quite similar to the sensitivity of the leukaemia HL-60 cells (Stefaniková *et al.* 2013) and L02 cells that are normal liver cells while the cells derived from hepatocellular carcinoma are more sensitive to butyrate (Wang *et al.* 2013). Sensitivity of the cells to either butyrate or vorinostat correlate well with an impact of the particular HDACi on acetylation of histone H3 (Wang *et al.* 2013; Mates *et al.* 2015). Pharmacokinetic measurements have revealed maximal serum concentration of vorinostat and vorinostat glucuronide after usual adult dose for cutaneous T-cell lymphoma to be 1.81 ± 0.70 and 3.62 ± 1.22 μmol/L, respectively (Ramalingam *et al.* 2007). There were no obvious differences between maximal serum concentration of vorinostat and vorinostat glucuronide on days 1 and 5 of the regular 5 days treatment regime. However, the sum of concentrations of both conjugated and non-conjugated vorinostat could be more than 5 μmol/L that is concentration of vorinostat associated with significant decrease of relative viability of SH-SY5Y cells. Thus, impact of vorinostat on relative cell survival could account for neuropathy that is often observed as adverse effect of the treatment of cutaneous T-cell lymphoma with vorinostat.

Impact of vorinostat on the induction of ER stress at the level of activation of ER stress sensor PERK in cancer cells was documented previously (Park *et al.* 2008) Butyrate treatment of the cells derived from colorectal carcinoma markedly enhanced the expression of ER stress-associated proteins, including GRP78, CHOP, PDI and IRE-1α (Zhang *et al.* 2016). Another study revealed that HDACi TSA specifically induce GRP78 (Baumeister *et al.* 2009) but it does not affect expression of other ER stress induced proteins including XBP1s and CHOP or HSP70 that is induced by proteasomal stress (Baumeister *et al.* 2009). In contrast, decreased expression of GRP78 was documented in leukaemia HL60 cells after the treatment with butyrate at millimolar concentrations for 48 h (Stefaniková *et al.* 2013). In the same study, unaltered expression of HSP70 was documented after the treatment of the HL-60 cells with butyrate. Treatment of rats and C6 glioma cells

with HDACi valproate was associated with increased expression of GRP78 but the expression of HSP70 was not elevated in the brains of rats treated with valproate (Wang *et al.* 2001). Since HRD1 is considered to be neuroprotective (Nomura *et al.* 2016), increased expression of HRD1 induced by vorinostat could explain the neuroprotective impact of vorinostat. However, expression of HRD1 was observed at a concentration of vorinostat 5μM that according to MTT assay is cytotoxic. Thus, neuroprotective impact of vorinostat and possibly other HDACi includes another mechanisms. In addition, it seems that HDACi mediated neuroprotection depends on type of neuronal injury (Park *et al.* 2025). For example, neuroprotective impact of vorinostat in a corticosterone-induced chronic stress model was attributed to the inhibition of caspase 3 via unclear mechanism (Athira *et al.* 2020) while low concentrations of butyrate protected SH-SY5Y cells treated with either TNF-α or amyloid β-peptide 25-35 through suppression of neuroinflammation and oxidative stress (Bayazid *et al.* 2021; Bayazid *et al.* 2023).

Conclusion

The negative impact of vorinostat on relative survival of neuronal cells could account for neuropathy that is often observed as an adverse effect of the treatment of cutaneous T-cell lymphoma with vorinostat. The potential of HDACi including vorinostat to induce ER stress proteins, HRD1 or GRP78, is probably not associated with neuproprotective effects of HDACi.

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Disclosures

The authors declare no conflicts of interests.

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