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Evaluation of the efficacy of valproic acid and suberoylanilide hydroxamic acid (vorinostat) in enhancing the effects of first-line tuberculosis drugs against intracellular *Mycobacterium tuberculosis*

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ABSTRACT

Background: New tuberculosis (TB) drug treatment regimens are urgently needed. This study evaluated the potential of the histone deacetylase inhibitors (HDIs) valproic acid (VPA) and suberoylanilide hydroxamic acid (SAHA) to enhance the effects of first-line anti-TB drugs against intracellular *Mycobacterium tuberculosis*.
Methods: M. tuberculosis H37Rv cultures were exposed to VPA or SAHA over 6 days, in the presence or absence of isoniazid (INH) and rifampicin (RIF). The efficacy of VPA and SAHA against intracellular *M. tuberculosis* with and without INH or RIF was tested by treating infected macrophages. Bactericidal activity was assessed by counting mycobacterial colony-forming units (CFU).
Results: VPA treatment exhibited superior bactericidal activity to SAHA (2-log CFU reduction), while both HDIs moderately improved the activity of RIF against extracellular *M. tuberculosis*. The bactericidal effect of VPA against intracellular *M. tuberculosis* was greater than that of SAHA (1-log CFU reduction) and equalled that of INH (1.5-log CFU reduction). INH/RIF and VPA/SAHA combination treatment inhibited intracellular *M. tuberculosis* survival in a shorter time span than monotherapy (3 days vs. 6 days).
Conclusions: VPA and SAHA have adjunctive potential to World Health Organization-recommended TB treatment regimens. Clinical evaluation of the two drugs with regard to reducing the treatment duration and improving treatment outcomes in TB is warranted.
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Introduction

Tuberculosis (TB) continues to cause 1.5 million deaths every year (WHO, 2015a). Although efforts to bring to the market new chemotherapeutic agents targeting the aetiological agent of TB (*Mycobacterium tuberculosis*) are ongoing, the protracted and expensive drug development process, coupled with a high attrition rate of new drug compounds, has hindered progress in the development of new anti-TB drugs. Efforts towards developing new TB treatment regimens to reduce the duration of treatment and improve treatment outcomes (mortality and long-term pulmonary complications (Manji et al., 2016)), particularly for drug-resistant TB, have focused attention on the repurposing of safe drugs commonly used in medical practice worldwide that are already approved by the United States Food and Drug Administration (FDA) for administration as adjuncts to TB therapy (Zumla et al., 2016). Some noteworthy examples include ibuprofen (Vilaplana et al., 2013), acetylsalicylic acid (Tobin et al., 2012; Byrne et al., 2007), simvastatin (Skerry et al., 2014), metformin (Singhal et al., 2014), and phenylbutyrate (Mily et al., 2015). These drugs may also act in a host-directed fashion (i.e., immune modulation) in concert with standard anti-mycobacterial drugs, thus engaging an additional avenue of ameliorating disease burden.

Various therapeutic agents licensed for non-TB indications appear to be promising against drug-sensitive as well as drug-resistant strains of *M. tuberculosis* (Kaufmann et al., 2014). Clinical testing of the histone deacetylase inhibitor (HDI) phenylbutyrate in patients with pulmonary TB has shown promising preliminary results, augmenting an inhibitory effect against *M. tuberculosis* growth with host macrophage immune responses (Mily et al., 2015; Coussens et al., 2015). HDIs increase the acetylation of lysine

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residues in histones, leading to chromosome unwinding and gene transcription, thus modifying gene expression (Haery et al., 2015).

Numerous HDIs are being actively explored for cancer therapy (Haery et al., 2015), among which are valproic acid (VPA) and suberoylanilide hydroxamic acid (SAHA/vorinostat). VPA is currently used as an anticonvulsant, and studies are simultaneously testing its clinical efficacy against several types of solid tumour and lymphoma (Haery et al., 2015). SAHA received FDA approval in 2006 for the treatment of cutaneous T-cell lymphoma (CTCL), while further clinical trials are underway to evaluate its adjunctive capacity against a myriad of solid tumours (Haery et al., 2015). Importantly, VPA and SAHA have also shown therapeutic potential against several infections. SAHA can trigger the reactivation of latent HIV-1 infection in human CD4 T cells (Archin et al., 2009), exposing viral progeny to antiretroviral drugs, and is currently under clinical investigation (clinicaltrials.gov identifier: NCT01319383, NCT01365065). SAHA has also shown activity against West Nile virus (WNV) replication and associated disease in experimental mice (Nelson et al., 2015). VPA can also promote latent HIV-1 reactivation (Zeng et al., 2014), and has been shown to induce the disruption of WNV infection of kidney cell lines derived from monkey and hamster, as well as the abrogation of herpes simplex virus 1 (HSV-1) infection of a human oligodendrocyte cell line (Crespillo et al., 2016).

This study evaluated the potential of VPA and SAHA as adjunct therapy for enhancing the effects of the two main first-line anti-TB drugs, namely isoniazid (INH) and rifampicin (RIF), against extracellular as well as intracellular *M. tuberculosis*.

Materials and methods

Reagents and culture media

Middlebrook 7H9 liquid medium supplemented with 10% oleic acid–albumin–dextrose–catalase (OADC), 2% glycerol, and 0.05% Tween 80 (7H9C), as well as Middlebrook 7H11 solid medium supplemented with 10% OADC and 2% glycerol (7H11C), were purchased from the Karolinska University Hospital substrate unit. RPMI Glutamax medium, foetal bovine serum (FBS), and antibiotics (penicillin/streptomycin) for tissue culture were purchased from Life Technologies. Phorbol myristate (PMA), VPA, SAHA, INH, and RIF were purchased from Sigma-Aldrich. SAHA, INH, and RIF stocks were prepared in dimethyl sulfoxide (DMSO), while VPA stocks were prepared in distilled water and stored at −20 °C.

Mycobacterial and THP-1 seed stocks

M. tuberculosis H37Rv was cultured in Middlebrook 7H9 medium supplemented with 10% OADC, 2% glycerol, and 0.05% Tween 80 (7H9C), and grown to mid to late log phase (OD_{600} 0.6–0.8). Mycobacterial cultures were first washed with phosphate buffered saline (PBS) containing 0.05% Tween 80 (PBST80) and resuspended in 7H9C medium supplemented with 16% glycerol stored at −80 °C. THP-1 human monocytes (kindly provided by Dr J. Muvva) were maintained in RPMI Glutamax medium supplemented with 10% FBS and antibiotics (R10+). Cells were washed with R10+ and resuspended in 90% FBS containing 10% DMSO for storage in liquid nitrogen tanks.

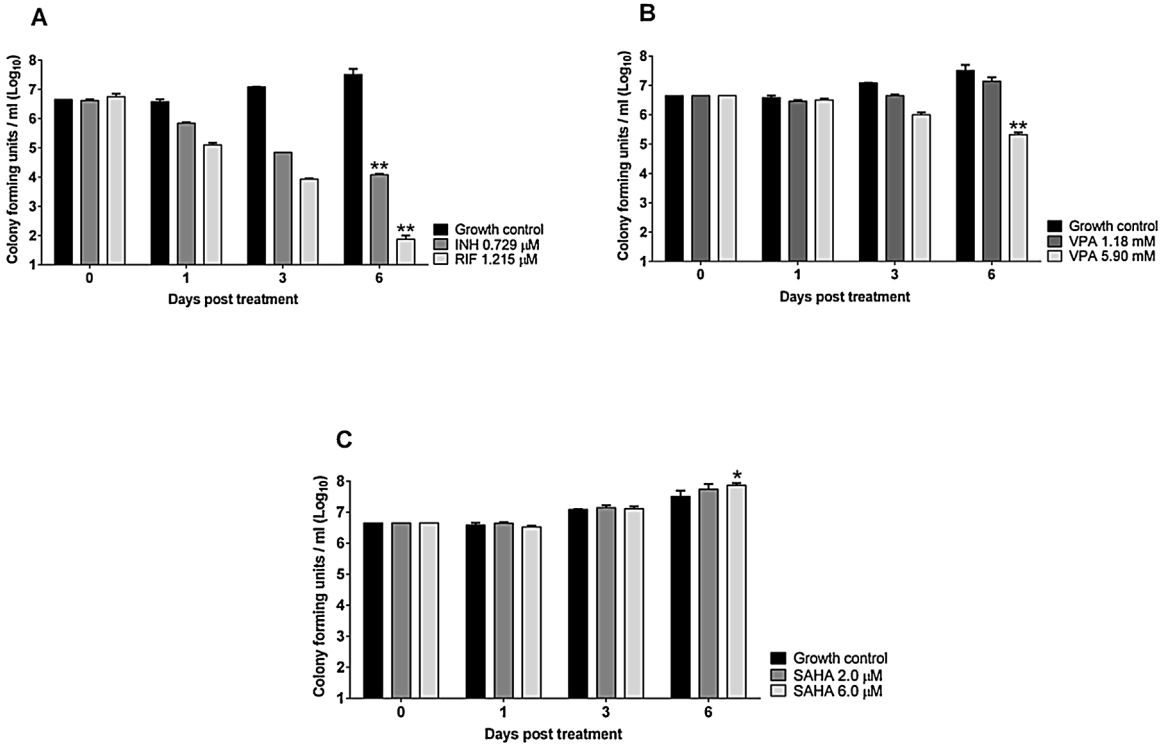

Figure 1. Anti-mycobacterial activity of isoniazid (INH), rifampicin (RIF), valproic acid (VPA), and suberoylanilide hydroxamic acid (SAHA) against *Mycobacterium tuberculosis* in liquid culture when exposed individually. Extracellular *M. tuberculosis* in mycobacterial growth medium were treated with INH or RIF (A), VPA at two different concentrations (1.18 mM and 5.90 mM) (B), or SAHA, also at two different concentrations (2.0 µM and 6.0 µM) (C). Concentrations of INH (0.729 µM) and RIF (1.215 µM) correspond to the World Health Organization-recommended standards (INH 0.1 µg/ml and RIF 1.0 µg/ml). The untreated growth control was used as the reference for bactericidal activity. Mean and SEM of two independent experiments analysed using two-way analysis of variance (ANOVA); $^{*}p < 0.05$, $^{**}p < 0.01$.

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