

HDAC Dynamics and GR Signaling: Neurobiological Insights and Antidepressant Potential

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Received date: July 03, 2024, **Accepted date:** October 01, 2024

Citation: Patel S, Chakravarty S. HDAC Dynamics and GR Signaling: Neurobiological Insights and Antidepressant Potential. J Ment Health Disord. 2024;4(1):57-62.

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Abstract

Histone deacetylases (HDACs) and glucocorticoid receptor (GR) signaling are critical in regulating gene expression and stress responses. Vorinostat, an HDAC inhibitor, shows significant promise in treating depression by modulating these pathways. This commentary explores HDAC inhibitor's mechanisms, therapeutic potential, and the challenges in clinical application. It compares the effects of various HDAC inhibitors on GR signaling and neuroplasticity, emphasizing the importance of personalized treatment approaches. Future research directions include identifying biomarkers for treatment response, developing selective HDAC inhibitors, and exploring combination therapies. This comprehensive overview aims to enhance understanding of HDAC inhibition's role in stress resilience and antidepressant mechanisms.

Keywords: Depression, HDAC inhibitors, MDD, Epigenetic therapies, Stress resilience, Biomarkers, Vorinostat

Introduction

The chronic social defeat stress model has been extensively utilized in mice to study resilience and vulnerability to stress-induced conditions such as depression [1]. This model involves subjecting mice to repeated social stress by exposing them to aggressive mice strain (CD1), leading to the development of phenotypic alterations like anhedonia, social avoidance, anxiety and despair in defeated mice while resilient mice remain immune to these effects. This model helps to understand the mechanisms underlying resilience and vulnerability to stress-related disorders like depression. Vorinostat, a histone deacetylase inhibitor shows promise as an antidepressant in the context of chronic social defeat stress [2]. The hyperacetylation induced by Vorinostat affects the expression of genes involved in cell cycle regulation, apoptosis and immune responses. Vorinostat exhibits a half-life of 60-100 minutes with a peak plasma concentration achieved approximately 90 minutes after oral administration [3]. Its metabolism primarily occurs through glucuronidation, hydrolysis and beta-oxidation with the majority of its metabolites excreted via urine. Notably Vorinostat is not

significantly metabolized by the cytochrome P450 system, reducing potential drug-drug interactions [4].

Histone deacetylases (HDACs) and glucocorticoid receptor (GR) signaling are critical in gene expression regulation and the body's response to stress [5]. This commentary examines the article "Differential modulation of GR signaling and HDACs in the development of resilient/vulnerable phenotype and antidepressant-like response of Vorinostat." The aim is to provide a comprehensive overview of HDAC inhibition with a focus on Vorinostat, its mechanisms, therapeutic potential and challenges in treating depression.

HDAC Isoforms in Depression

Vorinostat (suberoylanilide hydroxamic acid, SAHA) which was initially approved by FDA in 2006 for treating cutaneous T-cell lymphoma has shown promise in preclinical studies for its potential antidepressant effects [6]. Vorinostat with promising and broad applications in oncology has been recently investigated in several neurological disorders because of its ability to target multiple HDAC isoforms [7-

9]. Its mechanism of action in psychiatric disorders involves modulating the nuclear levels of glucocorticoid receptor (GR), HDAC3 and HDAC6 in the hippocampus which are associated with the development of resilience or vulnerability to stress [10]. Recent studies, including our own have highlighted Vorinostat's unique effects on neuroplasticity and stress resilience. Our research has shown that Vorinostat not only enhances synaptic plasticity but also alters the expression of genes involved in the stress response [10]. This suggests that Vorinostat may promote a resilient phenotype in the face of chronic stress, offering a novel angle for its use in treating stress-related disorders. Furthermore, comparative studies between Vorinostat and other HDAC inhibitors such as Valproic Acid and Trichostatin A reveal distinct differences in their efficacy and side effect profiles [7,9,11]. Unlike these other HDAC inhibitors, Vorinostat appears to offer a broader spectrum of action potentially beneficial for a wider range of patients.

Specific HDAC isoforms play pivotal roles in regulating depression pathways. HDAC isoforms exhibit region-specific roles in modulating pathways related to depression. For instance, one particular study highlighted a marked decrease in HDAC7 expression within the nucleus accumbens (NAc) of mice exposed to chronic social defeat stress. Interestingly this reduction was not observed for other HDACs like HDAC1, HDAC2 and HDAC6 indicating a specific role of HDAC7 in the observed depressive-like behaviors [12]. Furthermore, HDAC5 is highly expressed in brain regions implicated in mood regulation such as the prefrontal cortex and hippocampus. The inhibition of HDAC5 is shown to enhance the expression of these genes potentially reversing the maladaptive changes associated with depression. In our investigation cytoplasmic HDAC6 was specifically modulated in the hippocampus on Vorinostat administration to facilitate antidepressant like activity. Despite the well-known role of corticosterone [13], our studies in context to CSDS model arbitrarily indicated that Vorinostat does not regulate corticosterone levels while it still leads to enhanced behavioral outcomes in depressed mice [10]. The treatment of defeated mice with Vorinostat (VOR) for 14 days significantly improves neurobehavioral deficits induced by CSDS. In the SPT Vorinostat treatment reverses the reduced sucrose consumption seen in defeated mice. In the SI test, the percentage interaction time which gets reduced in defeated mice is improved with VOR treatment. We are yet to investigate Vorinostat on longer CSDS paradigms wherein we believe that increased duration of Vorinostat administration may lead to reduction in corticosterone levels along with positive behavioral functions.

Specific HDAC isoforms regulate inflammatory pathways in depression as well. Neuroinflammation plays a critical role in the pathophysiology of depression [14]. Vorinostat's anti-inflammatory effects are mediated through the modulation of immune cell activity and reduction of pro-inflammatory

cytokines [15]. By inhibiting HDACs Vorinostat reduces the expression of inflammatory markers and alters the activity of immune cells such as microglia and astrocytes [16,17]. This reduction in neuroinflammation contributes to the overall antidepressant effects of Vorinostat and projects its potential as a therapeutic approach for inflammation-related depression. A recent study showed that fluoxetine's antidepressant effects involve HDAC1 inhibition. The study demonstrated that LPS-induced depressive-like behaviors in mice were associated with increased HDAC1 expression and reduced eEF2 activity. Fluoxetine treatment ameliorated these effects by inhibiting HDAC1 thereby enhancing eEF2 activity and synaptogenesis. The use of Exifone (HDAC1 activator) reversed fluoxetine's antidepressant and anti-inflammatory effects, supporting the role of HDAC1 in neuroinflammation and depression [18]. HDAC1 and HDAC2 are involved in the formation of multiprotein complexes such as the NuRD complex which play essential roles in chromatin remodeling and gene repression [19]. This indicates the importance of targeting specific HDAC isoforms for better therapeutic outcomes.

Epigenetic Regulation and Neuroplasticity

Plasticity changes are crucial in depression and are often observed in CSDS models [1,20]. Resilience and vulnerability to stress are influenced by various factors including differences in neuroplasticity and molecular signaling. In resilient individuals there is enhanced activity in the ventral tegmental area (VTA)-nucleus accumbens (NAc) pathway, particularly involving brain-derived neurotrophic factor (BDNF) and its receptor TrkB [21,22]. These molecules support synaptic plasticity and adaptive responses to stress. In contrast susceptible individuals show altered BDNF-TrkB signaling contributing to maladaptive stress responses [23]. HDAC inhibitors (HDACi) enhance neuroplasticity by increasing histone acetylation facilitating the transcription of genes involved in synaptic plasticity and resilience. For instance, metformin's antidepressant effects are mediated through AMPK/CREB-mediated histone acetylation, enhancing BDNF expression [24]. A study involving the novel HDAC inhibitor IN14 demonstrated that it significantly increased histone acetylation, leading to improved synaptic plasticity and reduced depressive-like behaviors in animal models [25]. Chronic social defeat stress (CSDS) models showed that HDAC7 reduction in the nucleus accumbens is associated with depressive-like behaviors, suggesting a specific role for HDAC7 in regulating gene expression related to depression [12]. The upregulation of HDAC9 in hippocampal neurons inhibits the degradation of ANXA2, leading to depression-like behaviors [26]. HDAC inhibition by SCFAs like NaP can mitigate depressive-like behaviors by regulating gut microbiota and epigenetic mechanisms. NaP enhances histone acetylation leading to improved synaptic plasticity and neuroprotection. The study suggested the therapeutic potential of targeting HDACs through dietary interventions to enhance mental health and resilience to stress

[27]. The hippocampus plays a critical role in memory and emotional regulation and its function is significantly affected by stress [28]. In our studies with Vorinostat on CSDS we have consistently observed differences in the nuclear localization of GR, HDAC3 and HDAC6 between resilient and susceptible mice. In resilient mice there is maintenance of nuclear GR levels and balanced HDAC activity [10]. One proposed mechanistic insight as a result of the balanced HDAC6 would be enhanced neurogenesis in these mice. Susceptible mice show disrupted nuclear localization of these proteins leading to impaired hippocampal function and increased vulnerability to stress. Investigations on the neurogenesis aspect in these mice might provide further details of Vorinostat's mechanisms. Owing to improved synaptic connectivity our experiences with HDACi's in depression suggest that Vorinostat may be efficacious in the improvement of cognitive dysfunction as well in mice. Recent studies have tried to elucidate Vorinostat's role in cognition however investigations on CSDS model are very limited [29].

HDACs and GR Signaling

The glucocorticoid receptor (GR) signaling pathway plays a vital role in the body's stress response [30]. GRs activated by glucocorticoids, regulate numerous genes involved in stress response, inflammation and metabolism [31]. GRs are central mediators of the hypothalamus pituitary axis (HPA) influencing the body's response to stress [32]. Dysregulation of GR signaling is a hallmark of depression as chronic stress can lead to altered glucocorticoid levels and impaired feedback inhibition [33]. The relationship between HDACs and GR signaling involves complex epigenetic modifications influencing gene expression and affecting neuronal function and behavior [5]. In our experiments with chronic social defeat stress model Vorinostat treatment resulted in significant improvements in behavioral and molecular outcomes. GR is a pivotal mediator in the body's response to stress influencing gene expression by translocating to the nucleus upon activation. Our investigations have indicated a significant increase in cytoplasmic GR levels in resilient mice suggesting enhanced nuclear translocation in response to stress [34]. Conversely the reduced nuclear GR levels in defeated mice imply a deficiency in this translocation process potentially leading to inadequate transcriptional activation of genes associated with stress resilience. The study demonstrated that Vorinostat reduced depressive-like behaviors normalized GR signaling and increased histone acetylation levels [10]. In similar line a recent study demonstrated that early stress leads to reduced histone H3 acetylation at the GR promoter in the hippocampus impacting GR expression and contributing to depression-like behaviors [30]. It was recently shown that SIRT1, an NAD⁺-dependent deacetylase interacts with GR enhancing its signaling and mitigating depressive-like behaviors in a postpartum depression model. This study demonstrated that enhancing SIRT1-GR signaling can restore normal HPA axis function and reduce depressive symptoms

[35]. Several studies have demonstrated Vorinostat's neuroprotective effects in models of neurological disorders including Parkinson's disease (PD) and depression [36]. For instance in a PD model Entinostat, an HDAC inhibitor improved neurological functions, reduced levels of α -synuclein and increased expression of neuroprotective markers [36].

Differential Effects of Various HDAC Inhibitors

While Vorinostat shows significant promise, different HDAC inhibitors may have varying effects on GR signaling and neuroplasticity. Other HDAC inhibitors such as valproic acid (VPA) and trichostatin A (TSA) have also been explored in depression [37-39]. These inhibitors demonstrate similar neuroprotective effects by modulating histone acetylation and GR signaling. However the specific isoforms targeted by these inhibitors and their effects on gene expression and neuroplasticity differ from those of Vorinostat. Comparative studies indicate that while HDAC inhibitors like VPA and TSA share common mechanisms of enhancing histone acetylation [9], their specific effects on gene expression and neuroplasticity differ. VPA is known for its broad-spectrum HDAC inhibition leading to significant neuroprotective effects but also higher side effect risks due to lack of specificity [40]. A study conducted in 2017 indicated that TSA, targeting class I and II HDACs effectively modulates GR signaling and reduces depressive-like behaviors with potentially fewer side effects [41]. This specificity may provide a balanced treatment approach, reducing adverse effects while maintaining therapeutic efficacy.

Personalized Approaches to Treatment

The variability in response to HDAC inhibitors highlights the need for personalized treatment approaches. Factors like genetic background, individual stress response and comorbid conditions significantly influence the effectiveness of HDAC inhibition in treating depression [42]. Personalized medicine approaches considering these differences are essential for optimizing treatment outcomes. Future research should focus on identifying biomarkers predicting response to HDAC inhibitors and tailoring treatment protocols accordingly. Combination therapies incorporating HDAC inhibitors with other pharmacological or non-pharmacological interventions may increase therapeutic efficacy and reduce side effect risks [37,43]. Combining HDAC inhibitors with traditional antidepressants or cognitive-behavioral therapy (CBT) may provide a synergistic effect enhancing neuroplasticity and resilience while addressing underlying neurobiological mechanisms of depression [44]. HDAC research intersects with other areas of epigenetic modulation including DNA methylation and non-coding RNAs [45]. Combining HDAC inhibitors with DNA methylation inhibitors or targeting non-coding RNAs suggests new therapeutic possibilities.

A study in 2014 suggested that identifying biomarkers which predict response to HDAC inhibitors such as neurotrophic factors are crucial for personalized medicine [46]. Genetic and epigenetic markers can provide insights into individual variability in treatment response. Studies have identified several potential biomarkers such as changes in histone acetylation levels and expression patterns of GR-regulated genes which correlate with therapeutic outcomes [5]. Monitoring changes in histone acetylation and GR signaling can help assess treatment efficacy and adjust therapeutic protocols. Biomarkers such as BDNF levels, synaptic protein expression and GR nuclear translocation provide valuable information on the molecular effects of HDAC inhibition [10]. Research should focus on the role of different HDAC isoforms, the long-term effects of HDAC inhibition and the interaction between HDACs and other epigenetic regulators such as DNA methylation and non-coding RNAs.

Conclusion

HDAC inhibition by Vorinostat offers a promising therapeutic approach for treating depression by modulating GR signaling and enhancing neuroplasticity. However development of Vorinostat (and derivatives) as an antidepressant is in the early stage. HDACi target multiple isoforms and may increase the risk of side effects. Thus targeted HDACi's must be developed for efficacious pharmacotherapy. Personalized treatment approaches considering individual differences are essential for optimizing outcomes [47]. Further research into combination therapies and identifying predictive biomarkers can enhance the therapeutic potential of HDAC inhibitors in managing mood disorders.

Acknowledgements

SP wishes to acknowledge CSIR for providing doctoral fellowship during the present work. The Knowledge and Information Management (KIM) department of CSIR-IICT was duly acknowledged for generation institutional manuscript number IICT/Pubs./2024/234.

Declarations

Competing interest

The authors declare that they have no competing interests.

Author contributions

SP was involved in conceptualization, data curation, writing, original draft preparation and graphical editing. SC participated in data curation, formal analysis, funding acquisition, supervision, writing, reviewing and editing. Both the authors have seen and approved the final version of the manuscript being submitted.

Ethics approval

Not applicable.

Funding

This work was supported by SERB-POWER Fellowship to SC [SPF/2021/000045].

Data availability

Not applicable.

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