A Multi-Omics Therapeutic Approach using SAHA, SP600125, and Exercise to Modulate BDNF levels in Major Depressive Disorder

Krystal Grover[1], Kenzo Solano[1], Tracy Xu[1], Irma Lozica[1], Abramo Aziz Rizk[1], Mashraful Choudhury[1], Arjun Minhas[1], Jiya Khurana[1], and Ifeanyi Kennedy Nmecha[1]

[1]McMaster University, Canada

Major depressive disorder (MDD) is a leading cause of global disability, which is linked to reduced quality of life and comorbidities (e.g., diabetes, hypertension), and is burdened by a significant therapeutic knowledge gap. Brain-derived neurotrophic factor (BDNF), with its pro-apoptotic precursor (proBDNF) and neuroplasticity-promoting mature form (mBDNF), is dysregulated in MDD, where dysregulation of the proBDNF:mBDNF ratio serves as a biomarker and potential therapeutic target. Exercise has been documented to alleviate MDD symptoms partly by enhancing BDNF via epigenetic mechanisms. Inhibitors of the exercise metabolites β-hydroxybutyrate (BHB) and histone deacetylase 2 (HDAC2) (e.g., suberoylanilide hydroxamic acid (SAHA), a clinically approved drug) mimic this effect by suppressing BDNF-silencing HDAC2. However, excess proBDNF activates Jun N-terminal kinases (JNK)-p75 neurotrophin receptor apoptosis pathways, necessitating combinatorial therapies to optimize therapeutic effects. An example of combination therapy includes use of SAHA, a BHB mimic which upregulates BDNF transcription, with SP600125 which blocks JNK-mediated apoptosis.

In this review, we explore the use of multi-omics strategies aimed at restoring the proBDNF:mBDNF equilibrium, with some evidence supporting the combined use of BHB, SAHA, and SP600125 in polygenic models of major depressive disorder (MDD).We propose a series of multi-omics assays that can be used to validate this hypothesis: epigenomic via chromatin immunoprecipitation-sequence HDAC2 occupancy, transcriptomic via quantitative polymerase chain reaction for splice variants, proteomic via enzyme-linked immunosorbent assay for isoforms, and metabolomic via liquid chromatography-mass spectrometry for BHB. Moreover, assessing behavioural tests (e.g., forced swim) permits the further understanding of molecular changes that underlie symptom alleviation. This strategy bridges exercise-mimetic mechanisms (BHB/SAHA-driven HDAC2 inhibition) with precision medicine. We propose this scalable therapeutic blueprint by leveraging SAHA's clinical approval and SP600125's apoptotic mitigation. Future work must prioritize clinical trials to translate multi-omics insights into biomarker-guided human therapies.

Introduction

Major depressive disorder (MDD) is predicted to be the number one contributor to burden of disease worldwide by 2030.[1] In 2022, the prevalence of MDD among Canadians aged 15 years and older was estimated at 7.6%, equating to over 2.5 million people.[2] The annual economic burden of mental illness in Canada is estimated at over $50 billion, including healthcare costs and losses related to work absences, reduced productivity, and diminished quality of life.[2] MDD is characterised by feelings of guilt, worthlessness, loss of interest in pleasurable activities, and is associated with an increased risk of suicide. Furthermore, MDD's association with comorbidities such as diabetes and hypertension necessitates a need for deeper understanding of its mechanism of action.[3,4,5,6] Therefore, developing novel therapeutic targets and markers to help alleviate the burden of MDD on patient outcomes is crucial.

Current MDD-related therapies, including medications like fluoxetine, target various biomarkers such as cortisol, leptin, and interleukins.[2,7] One of the most promising proteomic markers is brain-derived neurotrophic factor

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(BDNF), with previous work supporting its ability to regulate neural plasticity and nervous system survival.[7,8,9] Importantly, BDNF comes in two forms; mature BDNF (mBDNF) and proBDNF, which play dichotomous roles in synaptic survival and plasticity. There is growing evidence highlighting the link between reduced serum mBDNF levels and a propensity for MDD progression, making it a promising biomarker for diagnosis and treatment.[6,10]

Intrinsically, mBDNF can be modulated through exercise, with evidence of it effectively ameliorating symptoms of MDD through its involvement in neural cellular functions, synaptic plasticity, and neurogenesis.[5,11,12,13] Additionally, prolonged exercise upregulates the production of β-hydroxybutyrate (BHB), a ketone body that can increase mBDNF expression by inhibiting histone deacetylases (HDACs).[5,11,12,13] Further research into mBDNF's potential as a therapeutic treatment may lead to more effective approaches for treating MDD.
Given the substantial evidence linking reduced levels of mBDNF with the pathophysiology of MDD, we propose that a multi-modal approach targeting key regulatory checkpoints of BDNF expression and function may offer a novel therapeutic avenue. Specifically, we hypothesize that concurrent modulation of BDNF transcription (via HDAC2 inhibition with suberoylanilide hydroxamic acid (SAHA)), translation (via Jun N-terminal kinases (JNK) inhibition with SP600125), and activity-dependent secretion (via BHB) will act synergistically to restore synaptic plasticity and reverse depression-like behavior in polygenic rodent models of MDD. This integrated strategy aims to overcome the limitations of single-target interventions and address the complex molecular deficits underpinning MDD.

Methods

To elucidate the molecular underpinnings of MDD and assess the therapeutic potential of modulating mBDNF, a targeted literature review was conducted across PubMed, Ovid, and ScienceDirect databases. The search prioritized primary research articles, systematic reviews, and meta-analyses published from 2015 onward, ensuring alignment with the rising global burden of MDD and advances in molecular research methodologies.

We included studies that examined the role of mBDNF in neuroplasticity and its modulation by interventions such as physical exercise, SAHA, SP600125, and BHB. Preference was given to studies employing omics-level analyses, specifically epigenomics, transcriptomics, proteomics, and metabolomics, to provide mechanistic depth and translational relevance.

Articles were screened for relevance based on their exploration of validated molecular markers of MDD and the integration of experimental or clinical data. We were especially interested in studies assessing exercise-induced modulation of BDNF, contextualized by evidence linking reduced serum BDNF levels to depressive phenotypes. This comprehensive synthesis facilitated a multi-dimensional understanding of BDNF pathway regulation in depression and identified potential nodes for therapeutic intervention.

Clinical Relevance of MDD

BDNF is a significant biomarker of MDD, with decreased mBDNF and increased proBDNF levels observed in affected patients.[8,14] Multiple studies have shown that exercise increases mBDNF levels through upregulation of protein synthesis via the inhibition of HDACs, garnering importance for HDAC inhibitors like SAHA in MDD treatment.[5,8,10,13]

mBDNF is known to promote neuronal survival and plasticity through the activation of several key signalling pathways by binding to the tropomyosin kinase receptor B (TrkB), an important receptor in MDD pathophysiology. Upon binding TrkB, mBDNF stimulates: the PI3K/mTOR pathway to enhance neuroplasticity, the mitogen-activated protein kinase-extracellular signal-regulated kinase pathway to support neurogenesis and cognitive resilience, and the phospholipase C-gamma (PLC-γ) pathway to regulate intracellular calcium for synaptic plasticity.15 Dysregulation of these pathways, particularly PLC-γ, has been linked to neuronal weakening and apoptosis, which contributes to the symptom presentation seen in MDD. Therefore, targeting these signalling cascades is essential for mBDNF-based MDD therapies.[16]

Conversely, upregulating the precursor proBDNF levels may increase neuronal cell apoptosis.[17] ProBDNF is known to bind to the p75 neurotrophin receptor (p75NTR) to induce apoptosis, growth cone retraction, and long-term depression.[18] This has critical implications for researchers and clinicians, as neural cell apoptosis compromises synaptic integrity by reducing

dendritic spine density and neurotransmitter signaling efficiency, mechanisms that have been implicated in the pathophysiology of neurodegenerative diseases like Alzheimer's disease and MDD.[19] Activation of the JNK pathway – a known promoter of oxidative stress and apoptosis – as a result of proBDNF binding to p75NTR can be inhibited with SP600125, negating the apoptotic side effects of proBDNF upregulation.[20] Interestingly, exercise plays a role in this approach by naturally enhancing mBDNF levels and priming neuroplastic pathways, thereby complementing the molecular effects of SAHA and SP600125. A combination therapy of SAHA, SP600125, and exercise presents a novel strategy for treating stress-related disorders and neurodegenerative diseases, including Alzheimer's disease.[19] Leveraging the benefits of exercise and pharmacological treatments while mitigating potential apoptotic side-effects could enhance neuroplasticity and cognitive resilience.[21] Further research to validate the evidence in clinical settings could offer a targeted and multifaceted intervention for conditions associated with BDNF dysregulation.

The role of Omics in the development of therapies targeting MDD

The link between exercise and BDNF inherently involves a multi-omics approach, emphasizing the value of various omics-level research. We see this at the epigenomic level, where BDNF transcription is tightly controlled by chromatin accessibility.[18] Among epigenomics studies, heritable gene expression changes have been identified that alter DNA expression, often via methylation or histone modification. Specifically, HDAC2 is an epigenetic silencer that binds to the promoter region of the BDNF gene and prevents the recruitment of certain transcriptional factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and cyclic adenosine monophosphate response element-binding protein (CREB).[22,23] Chromatin will bind more tightly due to the deacetylation of histones from HDAC, making transcription less accessible. Pharmacological tools altering the function of HDAC, such as SAHA, have been developed.[24] SAHA is a clinically approved HDAC2 inhibitor for cutaneous T-cell lymphoma that chelates zinc ion in the active site of HDAC2 and blocks its deacetylation function.[25] Therefore, SAHA maintains chromatin in a transcriptionally active state, enabling the genomic expression of BDNF.[26] While BHB levels fluctuate with metabolic activity, SAHA, a mimic of BHB, offers a more controlled means of promoting BDNF transcription, the impact of which can be measured with chromatin immunoprecipitation sequencing (ChIP-Seq) to quantify HDAC2 occupancy at BDNF promoter regions and track changes in acetylation patterns over time. Epigenomic regulation of BDNF through SAHA and exercise-induced BHB inhibiting HDAC2 presents a promising avenue for MDD treatment through BDNF upregulation.

Further, BHB connects BDNF in MDD at the level of metabolomics, the study of small-molecule metabolites representing the biochemical state of an organism or cell. BHB is a ketone body secreted from the liver and muscle tissue following exercise and can metabolically relieve HDAC-induced chromatin repression.[27] As a ketone body, it crosses the blood–brain barrier where it can act as a class I HDAC inhibitor, a group of enzymes primarily involved in altering gene expression in the brain, thereby increasing histone acetylation and access to BDNF promoter regions. Many other metabolites have been previously implicated in BDNF and exercise. El Hayek et al. showed lactate induces hippocampal BDNF expression via the sirtuin 1–peroxisome proliferator-activated receptor gamma coactivator 1-alpha signalling axis.[28] Additionally, Moon et al. linked elevated Cathepsin B levels in mice with increased hippocampal BDNF expression.[29] Though other metabolites have also been historically implicated (such as kynurenine and irisin), there are no recent studies to confirm such findings. Notably, among exercise-induced metabolites, BHB is particularly well-suited for experimental investigation due to its dual role in both metabolic and epigenetic regulation: as a metabolic intermediate of ketogenesis and as an endogenous inhibitor of class I HDACs. BHB directly influences chromatin accessibility at BDNF promoter regions, a clear link between metabolic shifts and epigenetic regulation.[30] Additionally, and quite importantly, lower circulating BHB levels and reduced mBDNF expression have been independently implicated in MDD. [9,31] BHB can be measured in both plasma and cerebrospinal fluid (CSF) using enzymatic assays or mass spectrometry, and its epigenetic effects can be evaluated through ChIP-Seq. Therefore, BHB represents a compelling metabolomic entry point for exploring the molecular basis of depression and potential exercise-mimetic therapies. BHB's bridge between metabolic and epigenetic BDNF regulation further strengthens its potential application as an MDD therapy.

At the transcriptomic level, MDD patients exhibit reduced pro/mature BDNF gene expression, leading to impaired neurogenesis, reduced hippocampal volume, and weakened synaptic plasticity. Exercise and antidepressants restore mBDNF mRNA levels, making it a potential transcriptional target.32 ProBDNF activation of the JNK pathway promotes pro-apoptotic gene transcription (e.g., BAX) while suppressing synaptic support genes (e.g., B-cell lymphoma 2 (BCL-2), postsynaptic density protein 95 (PSD-95)).[33] This JNK-mediated shift contributes to MDD's structural and functional deficits.[34] To counteract SAHA's potential upregulation of proBDNF transcription, SP600125 could be co-administered. This selective JNK inhibitor blocks JNK isoforms 1, 2, and 3, preventing the pro-apoptotic cascade from increased proBDNF-p75NTR signaling while retaining mBDNF's beneficial functions.

Proteomics, the large-scale study of proteins, captures BDNF's post-translational modifications, crucial for its function.[35] BDNF is translated as proBDNF, then cleaved into mBDNF by proteases like furin. In MDD, the proBDNF to mBDNF ratio shifts towards equality, promoting neurodegeneration,[36] unlike the healthy ratio.[37] This imbalance is measurable via Western blotting or enzyme-linked immunosorbent assays (ELISA) with isoform-specific antibodies, serving as a functional biomarker for disease progression and treatment efficacy. In neuropsychiatric disorders like MDD, proteomic alterations often involve downstream synaptic and apoptotic regulators: reduced PSD-95, essential for excitatory synapses38; downregulated BCL-2, promoting neuronal survival39; and increased caspase-3, activated downstream of proBDNF-p75NTR signaling, a common apoptosis biomarker and a critical readout of the consequences of an altered proBDNF:mBDNF ratio.[40] While epigenomic and transcriptomic findings suggest BDNF's pathological involvement, only proteomic analysis confirms its functional form. Measuring caspase-3 evaluates successful inhibition of proBDNF-induced apoptosis.

Proposed Multi-Omics Experiment in MDD Mouse Models

The current paper presents a synthesis of the extant literature that explores the mechanistic role of BDNF in MDD, with a particular focus on exercise and its molecular mediators. Particularly, evidence frames mBDNF as a central and tractable therapeutic target in MDD. While previous research has often treated these omics layers in isolation, our review highlights the need for integrative approaches that capture the interplay between metabolic signals like BHB, chromatin remodeling enzymes such as HDAC2, transcriptomic shifts in apoptotic regulators, and proteomic imbalances in proBDNF:mBDNF ratios. To move from theoretical integration to applied investigation, we propose a model experiment using polygenic mouse strains of MDD. These mice could be treated with BHB, SAHA, and SP600125, alone and in combination. Molecular outcomes would be measured as follows: BHB in plasma or CSF (metabolomics), HDAC2 promoter occupancy via ChIP-Seq (epigenomics), expression of BDNF and JNK-pathway genes via quantitative polymerase chain reaction (transcriptomics), and BDNF and caspase-3 via ELISA (proteomics). This approach would evaluate the efficacy of exercise-mimetic and pharmacological interventions combination as a potential novel treatment regimen for MDD patients.

This proposed experiment serves as one possible extension of this framework and, more importantly, outlines the role of multi-omics thinking in informing experimental design and clarifying the mechanisms underlying complex psychiatric conditions like MDD. By examining BDNF regulation across metabolomic, epigenomic, transcriptomic, and proteomic layers, this review highlights the importance of systems-level approaches in identifying precise therapeutic targets. As the field moves toward integrative, mechanism-based psychiatry, multi-omics research offers a powerful lens through which to untangle and leverage the molecular heterogeneity of depression.

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