COMMENT

Exercise mimetics as unexplored therapeutics for treating depression

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PHYSICAL ACTIVITY AND DEPRESSION

Depressive disorders are the second leading cause of disability globally [1]. Population-level research has demonstrated that even achieving half the recommended level of physical activity is associated with a 18% lower risk of depression [2]. For those with non-severe depression, exercise has proven to be a similarly effective treatment when compared to traditional first-line measures such as medications and psychotherapy [3, 4]. Moreover, depressed individuals face barriers such as low energy, lack of motivation, anhedonia, socio-economic pressures, co-morbidities, inexperience, and time constraints which can hinder engagement as well as long term adherence to exercise regimes [5]. For example, adherence is lower and drop out rates are higher for exercise interventions than medications, despite the side effects of antidepressant medications [3]. Given this, pharmacological interventions which mimic the effects of endurance exercise on skeletal muscle characteristics may represent a novel class of therapeutics for treating depression.

THE POTENTIAL OF EXERCISE MIMETICS IN DEPRESSION

Compounds that reproduce the effects of endurance exercise on skeletal muscle are referred to, albeit controversially, as exercise mimetics and exercise pills. These compounds are powerful activators of pivotal signalling pathways in skeletal muscle that modify the contractile and metabolic properties of muscle fibres to become slower and more oxidative without requiring actual endurance exercise [6]. They include natural substances and synthetic drugs (e.g. AICAR, GW501516, metformin, resveratrol, NAD+ boosters, urolithin A, etc.) which can also modify the type and amount of molecules secreted by skeletal muscle into the bloodstream, thus affecting the complement of the myosecretome. While exercise mimetics demonstrate antidepressant-like effects in animal models (whose behavioural assays have limited construct validity for human depression), supporting evidence in humans is still limited [7, 8]. In animal models, exercise mimetics have demonstrated the potential to modulate underlying neurobiological mechanisms such as neurotransmitter levels, inflammation, and hypothalamic-pituitary (HPA) axis dysregulation, among others, which were associated with the alleviation of depressive-like behaviors [6–8]. The aforementioned changes attributed to exercise mimetics overlap in the pathophysiology of depression in humans and may thus have potential as an unexplored treatment option.

Key molecular pathways

As mentioned above, exercise mimetics activate key molecular pathways known to be critical regulators of the phenotype of skeletal muscle fibers (see Table 1 for a list of exercise mimetics). More specifically, exercise mimetics target AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor delta (PPARδ), Sirtuin 1 (SIRT1) as well as their downstream effectors. AMPK is a cellular energy sensor and protein kinase that activates energy-producing pathways and suppresses energy consuming ones, while PPARδ is a nuclear receptor that regulates fatty acid metabolism, glucose homeostasis and inflammation. On the other hand, SIRT1 acts as a deacetylase and removes acetyl groups on proteins that include histone and non-histone targets, thereby modifying their function. Activation of the AMPK, PPARδ and SIRT1 pathways enhance mitochondrial function and energy metabolism, both of which are impaired in depression [9]. Similarly, PGC-1α is a regulator protein that controls mitochondrial biogenesis, energy homeostasis, and oxidative metabolism. Exercise mimetics upregulate PGC-1α in skeletal muscle and promote its nuclear accumulation which, in turn, results in modulations of kynurenine metabolism. Interestingly, kynurenine is a tryptophan metabolite generated under stress and elevated kynurenine levels are associated with neurotoxic metabolites and depression [10]. Of relevance, elevated PGC-1α in skeletal muscle fibres shifts this metabolism profile towards the anti-inflammatory kynurenic acid, which has demonstrated antidepressant effects in animal models [11]. Collectively, the activation of these signalling molecules promote the expression of a slower, more oxidative muscle phenotype as seen following endurance training. Moreover, activation of these pathways and this resulting fiber type switch alter the molecular signature of the myosecretome with potential beneficial impact at sites distant from muscle, including the brain.

Modulation of the myosecretome

Molecules that are produced and secreted by muscle fibers include a diverse array of signalling molecules including cytokines, peptides, growth factors, lipids and small RNAs. Their secretion occurs through both conventional pathways, involving the endoplasmic reticulum and Golgi apparatus, and unconventional

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Table 1. Exercise mimetics, signalling pathways, and possible crosstalk with the brain.

Compound	Signalling Pathways	Crosstalk with Brain
Pharmacological exercise mimetics		
AICAR	Activates AMPK → PGC-1α, mitochondrial biogenesis	↑ BDNF, ↑ synaptic plasticity
Metformin	Inhibits mitochondrial complex I → AMPK activation	Crosses BBB, ↑ AMPK and BDNF, ↓ neuroinflammation
GW501516	Activates PPARδ → fatty acid oxidation	↓ Neuroinflammation
NAD^+ boosters (e.g. nicotinamide riboside)	↑ NAD^+ → activates SIRT1, AMPK, and mitochondrial biogenesis	↑ BDNF, neurogenesis, and mitochondrial function
Urolithin A	Promotes mitophagy, activates AMPK-PGC-1α, mitochondrial biogenesis	↓ Neuroinflammation, ↑ synaptic plasticity
Natural compounds with exercise-mimetic properties		
Resveratrol	Activates SIRT1, AMPK-PGC-1α axis, antioxidant signalling	Crosses BBB, ↑ BDNF, neurogenesis and plasticity
Quercetin	Activates AMPK, ↑ mitochondrial biogenesis, antioxidant via Nrf2	Crosses BBB, ↑ BDNF, ↓ neuroinflammation
Epicatechin	Activates AMPK, enhances mitochondrial biogenesis, ↑ NO signalling	Crosses BBB, ↑ BDNF, ↑ angiogenesis
Curcumin	Activates AMPK, Nrf2, inhibits NF-κB → anti-inflammatory and antioxidant	Crosses BBB, ↑ BDNF, modulates neurotransmitters, ↓ neuroinflammation
Berberine	Activates AMPK, improves mitochondrial function, ↓ inflammation	Crosses BBB, ↑ BDNF, ↓ neuroinflammation
Omega-3 fatty acids (EPA, DHA)	Activates PPARs, GPR40/120, anti-inflammatory, modulates membrane signalling	Incorporated in brain membranes, ↑ BDNF, ↓ neuroinflammation
Spermidine	Induces autophagy, improves mitochondrial quality, AMPK activation	Crosses BBB, enhances synaptic plasticity, improves memory, neuroprotective
Ginsenosides (e.g. Rg1, Rb1)	Activates AMPK, PI3K/Akt, ERK, antioxidant and neurotrophic signalling	Crosses BBB, ↑ BDNF, ↑ neurogenesis

AICAR 5-Aminoimidazole-4-carboxamide ribonucleotide, *AMPK* AMP-activated protein kinase, *BBB* blood-brain barrier, *BDNF* Brain-Derived Neurotrophic Factor, *ERK* Extracellular signal-regulated kinases, *NO* Nitric oxide, *PGC-1α* Peroxisome proliferator-activated receptor-gamma coactivator 1-alpha, *SIRT1* Sirtuin 1
GW501516 is not suitable for clinical use due to safety concerns (potential carcinogenicity).

pathways such as the direct translocation of extracellular vesicles. These vesicles include exosomes and microvesicles, generated via the exocytosis of multivesicular bodies and membrane blebbing, respectively. Once in the bloodstream, these molecules exert autocrine, paracrine or endocrine effects [12]. In the context of the current discussion, these molecules also mediate communication between muscle fibers and other organs, including the brain. Low basal myokine levels have been associated with impaired quality of life and depressive symptoms [13]. The neurotrophic hypothesis of depression posits that depression stems from a deficit in brain-derived neurotrophic factor (BDNF) and impaired neuronal plasticity, leading to neuronal damage, atrophy, and inflammation, particularly in the hippocampus [14]. Exercise is a remarkably robust stimulus for BDNF release [15]. Induction of the myokine irisin by exercise mimetics increases the production of BDNF and reduces symptoms of depression [8]. Various other myokines implicated in depression (e.g., IL-6, IL-15, musclin, cathepsin B), which regulate inflammation and metabolism, are modulated by exercise mimetics, and mediate symptoms of depression in animal models [7].

Muscle phenotype changes

The concept we present here is that following chronic administration of exercise mimetics, skeletal muscle fibers will alter their contractile and metabolic profile which will cause changes in: i) the composition of the myosecretome; ii) the relative amount of each secreted molecule; and iii) the route and pattern of secretion, all towards a more therapeutic profile for depression, thereby reproducing the effects, at least partially, of long-term endurance training (Fig. 1). In this notion, skeletal muscle, which constitutes ~40-50% of the body mass in adults, represents a central therapeutic platform to mediate the potential beneficial impact of exercise mimetics on depression [16]. In depression, these changes may thus enhance the "muscle-brain axis" via amplification of beneficial signalling. In addition to these signalling benefits across tissues, the resistance-mediated effects of exercise mimetics can increase muscle mass and strength, which are also associated with reduced depressive symptoms [17]. In this scenario, muscle fibers with slow, oxidative dominance secrete a more neuroprotective complement of molecules, which may be associated with improved metabolic homeostasis, mitochondrial function and epigenetic changes, thereby contributing to long-term mood stabilization.

RATIONALE FOR THE PROPOSED CAUSAL DIRECTION

As a large portion of the above mechanistic effects of exercise mimetics, and their potential benefits for treating depression, rely on correlational rather than causal evidence, we here provide our rationale for the muscle to brain direction of causality of the therapeutic effects of exercise mimetics in the treatment of depression. First, experimental exercise interventions demonstrate that increasing myokine and kynurenic acid production (from kynurenine via muscle-specific upregulation of PGC-1α) through physical activity alleviates depressive behaviours in mice [8, 11]. Second, temporal sequencing in these processes demonstrates that myokine secretion and kynurenine metabolism occur rapidly in response to muscle activation, which precede observable improvement in brain function or mood [11, 18]. This suggests that myokines and kynurenine metabolism function as upstream

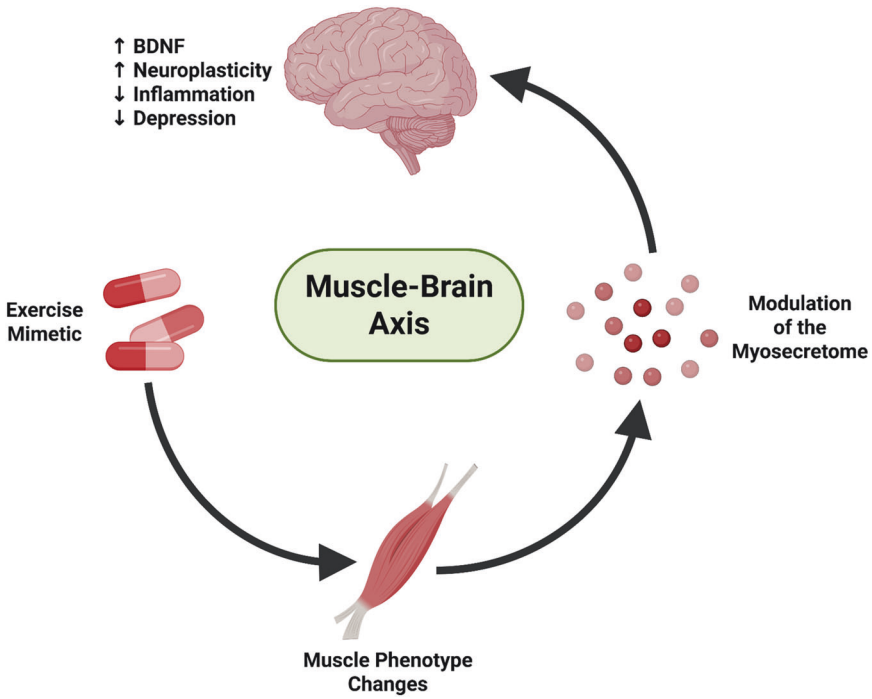

Fig. 1 The potential impact of exercise mimetics on muscle phenotype, the myosecretome and mental health. Created in BioRender. Fabiano, N. (2025) https://BioRender.com/1o41jn2.

initiators, rather than solely downstream consequences of depression. Third, dose-response relationships further provide support whereby higher-intensity or prolonged exercise leads to greater myokine release and higher PGC-1α activity (leading to greater kynurenine clearance), and increased antidepressant outcomes [3, 18–20]. However, this rationale does not preclude the element of reverse causality which is likely concurrently at play whereby depression itself may also alter myokine and kynurenine metabolism through inactivity, inflammation and neuroendocrine changes.

THE FUTURE OF EXERCISE MIMETICS IN DEPRESSION

Exercise mimetics may thus have potential in both the treatment and prevention of depression. With regards to prevention, high risk groups with functional impairments (i.e., post-stroke, elderly populations, or significant comorbidities), who may not be able to engage in traditional programs of chronic exercise training, may be ideal candidates for treatment with exercise mimetics. Although exercise has demonstrated efficacy comparable to medications and therapy in depression, multiple factors as stated above serve as barriers to engagement. Therefore, exercise mimetics could serve as a substitute helping to compensate for limited regular physical activity, or perhaps provide additive or even synergistic therapeutic benefits when combined with traditional exercise.

There is limited research focused on this question in humans. A systematic review was conducted [21] to determine the impact of metformin on depressive symptoms, which only found one randomized controlled trial (RCT) of metformin versus placebo in patients ($n = 58$) with depression and type 2 diabetes. After 24 weeks of treatment, metformin was associated with significant reductions in depressive symptoms as measured by the Montgomery–Åsberg Depression Rating Scale (MADRS) ($F_{1,112} = 26.43$; $P < 0.001$) and Hamilton Rating Scales for Depression (HRSD-17) ($F_{1,112} = 27.61$; $P < 0.001$) [22]. Metformin, although traditionally seen as a first-line medication for diabetes, also functions as an AMPK activator and can generally be considered as an exercise mimetic [21]. Another systematic review and meta-analysis of RCTs in a heterogenous non-depressed population (4 studies, 225 patients) found that resveratrol had a positive, yet statistically insignificant impact on mood (weighted mean difference [WMD] −0.6, 95% CI: −1.3 to 0.06 [$P = 0.2$]). However, this study is limited by small sample size with examination of a non-depressed patient population [23]. Nonetheless, as depression is common in many populations with other medical conditions, post-hoc analyses can be conducted based on existing trial data and synthesized in meta-analyses. Although a clinical trial (NCT03384329) evaluating the short-term (one month) effects of daily doses of resveratrol on depression was conducted several years ago, the results are not yet available.

Obviously, the current evidence of exercise mimetics in human populations is inconclusive. Despite this, the mixed above results have important implications for our theory which posits a central role for muscle-brain signalling via modulation of the myosecretome and key molecular pathways. First, the antidepressant findings of metformin in a depressed population with type 2 diabetes may be confounded by its broader metabolic benefits (such as improved glucose regulation and enhanced insulin sensitivity) [21]. While these metabolic effects may indirectly support muscle-brain crosstalk, they do not isolate the specific contribution of skeletal muscle adaptations or myosecretome changes. Second, the non-significant positive trends with resveratrol (a SIRT1 and AMPK-PGC-1α activator) in a non-depressed population indicate potential mood-enhancing effects, however the small sample and heterogeneous cohorts limit interpretation [23]. If future trials with more effective and targeted compounds (Table 1) yield null effects, this may thus highlight i) that muscle-brain signalling is necessary but not sufficient for antidepressant efficacy, ii) identify the importance of patient selection (i.e., metabolic impairments, high inflammatory levels, low baseline physical activity, or specific biomarkers of myokine or kynurenine dysregulation), and/or iii) underscore the need for combinatorial approaches (such as pairing exercise mimetics with antidepressants, therapy or exercise). Therefore, and based on the foregoing discussion and therapeutic model that we present here, it seems

highly warranted and timely to begin examining and dissecting systematically the potential of exercise mimetics via modulation of the myosecretome in the quest to provide novel and effective treatment avenues for improving non-severe depression.

CONCLUSION

In summary, exercise mimetics appear promising as a basis for novel and efficacious treatments for non-severe depression yet, their therapeutic potential remains underappreciated and, hence, under-investigated. There is a significant body of literature which clearly demonstrates that exercise is an equally effective treatment for non-severe depression when compared to traditional first-line measures such as antidepressants or therapy [3]. Exercise mimetics replicate certain skeletal muscle-specific adaptations typically induced by endurance training yet, they fail to provide the full spectrum of benefits associated with regular exercise training including cardio-pulmonary adaptations. Although these biological benefits are partially replicated, exercise mimetics fail to also replicate the social and psychological impacts of exercise, which may be crucial factors with regards to antidepressant effects. Further, a large portion of the mechanistic effects rely on correlational rather than causal evidence. Therefore, future research should focus on investigating the role of exercise mimetics both in the treatment (monotherapy or combination) and prevention of depression, and identify target groups which would benefit most.

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AUTHOR CONTRIBUTIONS

NF and BJJ conceptualized the idea. BJJ and JGF provided supervision. NF wrote the original draft of the manuscript. NF, JGF, ARC and BJJ contributed to the review and editing of the final manuscript and approved it for submission.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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