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Molecular origin and biological effects of exercise mimetics

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ABSTRACT

With the rapid development of sports science and molecular biology technology, academia refers to molecules or microorganisms that mimic or enhance the beneficial effects of exercise on the body, called "exercise mimetics." This review aims to clarify the concept and development history of exercise mimetics, and to define the concept of exercise mimetics by summarizing its characteristics and functions. Candidate molecules and drug targets for exercise mimetics are summarized, and the relationship between exercise mimetics and exercise is explained, as well as the targeting system and function of exercise mimetics. The main targeting systems for exercise mimetics are the exercise system, circulatory system, endocrine system, endocrine system, and nervous system, while the immune system is potential targeting systems. Finally, future research directions for exercise mimetics are discussed.

1. Introduction

Currently, new drug development is becoming increasingly difficult and time-consuming. According to reports, the number of new drugs that make it to market for every $1 billion invested is halved every nine years, and is stuck in the 'anti-Moore's Law' dilemma.[1] The 'anti--Moore's Law', signifying that the returns from drug development are significantly lower than the capital invested. Exercise mimetics, an avant-garde paradigm in drug development, harness the advantageous outcomes derived from established physical activities. Through the integration of artificial intelligence (AI) technology, this approach not only provides novel perspectives in drug discovery but also presents a promising trajectory to confront the limitations posed by the 'anti--Moore's Law'. It is well known that 'exercise is medicine' (EIM), and can be involved in the prevention and treatment of up to 26 diseases such as obesity, diabetes, and cognitive dysfunction.[2–4] Suitable exercise can induce adaptive changes in the body, producing health benefits that involve numerous cellular and molecular changes, countless intricate biochemical reactions, and interactions between tissue and organs.[5–7] These molecules or microorganisms involved in adaptation may provide inspiration for pharmaceuticals.

The concept of 'Enviromimetics' was introduced 20 years ago and refers to new therapies that are able to mimic or enhance beneficial environmental stimuli through complementary approaches based on gene-environment interactions and experience-dependent molecular mechanisms of plasticity, which can be broadly engaged in the treatment of disease.[8,9] Based on this, in June 2021, Gubert proposed a new drug development approach that designs adaptive changes in the health benefits induced by exercise as efficacy substances for preventing and treating certain specific diseases, called 'Exercise Mimetics'.[7] Therefore, it is presumed that 'Exercise Mimetics' is a subclass of 'Enviromimetics'. Studies have designed a transmembrane protein 130 (GP130) ligand small molecule IC7Fc based on the characteristics of interleukin 6 (IL-6) and ciliary neurotrophic factor (CNTF), which removed one GP130 binding site in IL-6 and replaced it with a leukemia inhibitory factor (LIF) receptor binding site in CNTF, and then fused it with the immunoglobulin G (IgG) Fc domain. IC7Fc has CNTF morphology and IL-6 receptor-dependent features, and is used to treat type 2 diabetes, and has passed preclinical trials. This achievement was published in the journal Nature and recommended on its public account.[10] This is the first potential drug developed and validated using the exercise mimetic development strategy. In addition, studies have found that aerobic exercise can upregulate the expression of $CD8^+$ T cells and IL-15Rα sensitive to interleukin 15 (IL-15), leading to the enrichment of $CD8^+$ T cells and IL-15Rα on pancreatic cancer cells and killing tumor cells. Novartis developed an IL-15 agonist, NIZ985, based on this mechanism, which can simulate the effect of exercise to enhance the IL-15/IL-15Rα signaling pathway, reduce potential inflammatory reactions, and produce sustained anti-tumor effects.[11] This is the first report of using exercise mimetics to treat cancer. It is imperative to recognize that the realm of exercise mimetics is currently in its nascent stages, marked by an absence of conclusive determinations regarding

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the cause-and-effect relationships between candidate molecules and established drug targets. Consequently, exercise mimetics currently represent a conceptual framework, and only the two studies mentioned earlier have conducted direct clinical trials under this guiding principle. Both of these studies have exclusively reported results from animal experiments, with no disclosed outcomes from human trials. Additionally, as of now, no exercise mimetic drugs have progressed through Phase III clinical trials to attain market approval. This underscores that research on exercise mimetics remains in its early developmental phase, with no definitive conclusions drawn regarding the efficacy and potential adverse effects of these compounds. It implies that the transition from exercise mimetics to "exercise pills" has not been fully actualized. Future endeavors should prioritize the expansion of clinical research to refine and authenticate this research paradigm.

In summary, 'Exercise Mimetics' is a subclass of 'Enviromimetics', the development strategy of exercise mimetics can provide new directions for new drug development, which can help break the 'anti-Moore's Law' of drug discovery and accelerate the speed of drug development. This review aims to clarify the concept of exercise mimetics, trace its developmental history, and provide a comprehensive literature review on its candidate molecule sources, established drug targets, and biological mechanisms. By systematically collecting relevant literature in the field of exercise mimetics, we intend to integrate distinctive features from these sources to enhance the understanding of exercise mimetics. Finally, it will explore the application and trends of AI and bioinformatics tools in the development of exercise mimetics.

2. Overview of exercise mimetics

Exercise mimetics are a proposed class of therapeutics that specifically mimic or enhance the therapeutic effects of exercise.[7] Exercise mimetics mainly benefit health through three ways: synthesizing myokines, regulating signaling pathways, and targeting small molecule targets (Table 1).

2.1. Myokines

The process by which certain factors produced in muscles during exercise act on various tissues such as the brain, liver, and adipose tissue through endocrine mechanisms, exerting beneficial effects on overall health, is referred to as the "work stimulus," "work stimulus," "work factor," or "exercise factor".[31,32] Pedersen's seminal work quantified a striking surge, approximately 100–150 times the baseline, in IL-6 concentrations within the bodies of marathon runners immediately post-race, predominantly originating from active musculature. Subsequent investigations unveiled the multifaceted impacts of IL-6, encompassing heightened glucose absorption and insulin responsiveness in the healthful populace, augmentation of skeletal muscle mass and strength, and facilitation of adipose tissue breakdown coupled with enhanced fatty acid oxidation. This groundbreaking revelation substantiates, for the first time, a substantial escalation of IL-6 within functioning muscles post-exercise, conclusively affirming the presence of muscle-derived IL-6.[12] Therefore, Pedersen boldly proposed that IL-6 produced by working muscles during exercise is considered a "myokine" and named it as such.[31,33,34] In January 2012, Nature reported the discovery of a PGC1-α-dependent myokine called irisin, and confirmed that both mice and humans promote the secretion of irisin after exercise, acting on white adipose tissue, stimulating the expression of uncoupling protein 1 (UCP1) and brown fat-like development, improving glucose homeostasis and preventing obesity.[15] This investigation unveiled escalated extracellular heat shock protein 90α (eHsp90α) levels in the interstitial fluid and plasma of murine muscle tissues post-exercise. Notably, it elucidated the binding capacity of eHsp90α to integrin αVβ5, inducing conformational alterations in Irisin. The activated Irisin, in turn, engages integrin through high-affinity binding sites, initiating signal transmission via the Hsp90α/αV/b5 complex. These findings offer crucial insights into the functional mechanism of Irisin, thereby contributing to the advancement of exercise mimetics grounded in Irisin35. Therefore, This is an extension and expansion of the "myokine" family. In October 2016, Febbraio referred to more than 200 myokines that mainly promote health as a myokinome.[20]

2.2. Signaling pathways and small molecular targets

The skeletal muscle signaling pathway is an important target for exercise mimetics. Exercise training activates the interaction between AMPK and PPAR-δ agonists, participating in the regulation of muscle fiber metabolism, contraction, and control of the metabolic phenotype of muscle fibers. Moreover, even in the absence of exercise, oral administration of the AMPK agonist AICAR can target the AMPK-PPARδ pathway to enhance training adaptability and increase endurance, making AMPK and PPAR-δ considered crucial candidate molecules for exercise mimetics.[14] It is well-established that various forms of exercise have been demonstrated to increase adiponectin mRNA expression and monomeric protein levels of adiponectin, accompanied by an elevation in AdipoR1 protein levels.[36–38] Adiponectin activates AMPK/SIRT1/PGC-1α through its receptor AdipoR1 in skeletal muscle, enhancing insulin sensitivity and exercise endurance in obese diabetic mice. Additionally, muscle-specific upregulation of AdipoR1 leads to the restoration of mitochondrial-related gene expression, similar to the recovery observed in mice subjected to exercise under high-fat diet conditions. This suggests that upregulation of AdipoR1 is a potential candidate for exercise mimetics.[24] In addition, Li et al.[18] proposed to use signaling pathway molecules activated by exercise as pharmacological targets for the development of "exercise pills" that can improve fatty acid oxidation, skeletal muscle fiber type transformation, mitochondrial biogenesis, angiogenesis, and exercise capacity. As is well known, exercise has the ability to increase the expression of mitochondrial PGC-1α and promote mitochondrial biogenesis.[39,40] Further research found that the PGC-1 gene can encode the PGC-1alpha4 protein, and found that in a mouse model of skeletal muscle-specific PGC-1alpha4 overexpression, it can specifically induce mouse IGF-1, inhibit myostatin, and resist cancer cachexia-induced muscle atrophy, while significantly improving skeletal muscle strength and mass.[16] Nine years later, Ruas discovered that after eight weeks of voluntary wheel running exercise, skeletal muscle neurotrophin (NRTN) expression increased, and by constructing a mouse model of NRTN overexpression (human alpha-skeletal actin neurotrophin, HSA-NRTN), it was found that compared with wild-type mice, HSA-NRTN mice had higher integrity of neuromuscular junctions, more stable muscle nerve fiber structure, and optimized local energy metabolism function of muscles, significantly improving endurance, speed, and delaying degenerative motor neuron diseases. In addition, HSN-NRTN mice significantly reduced body weight and improved glucose tolerance by affecting lean body weight and reducing subcutaneous fat accumulation.[27] Therefore, the skeletal muscle PGC-1 gene and NRTN is also considered a potential candidate molecule for exercise mimetics. In addition, some specific small molecules that promote overall health are also considered as candidate molecular targets for exercise mimetics. For example, in March 2022, Leiter reported in Cell Metabolism that acute treadmill exercise for four days significantly upregulated the expression of selenoprotein P (SEPP1) in mouse plasma, promoting hippocampal neural progenitor cell proliferation and adult neurogenesis without affecting cell apoptosis. Further research found that exogenous selenium supplementation significantly improved hippocampus-dependent spatial learning and memory ability in mice, indicating that selenium may be one of the potential targets for treating hippocampus-related neurodegenerative and cognitive decline diseases.[29] In June 2022, Li reported in Nature that mice and humans after exercise showed increased levels of irisin, a myokine produced by skeletal muscles, in blood circulation. Irisin was found to stimulate beige adipocyte formation and improve metabolic health, suggesting that irisin could be a potential target for the treatment of metabolic

Table 1
The research history of the exercise mimetics.

Author/Year	Journal/Article type	Article	Research results	Target
Ostrowski et al. (1998)[12]	The Journal of physiology; Article	Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running	The concentrations of IL-6 were measured in marathon runners before, immediately after, and 2 h after the race. It was found that the IL-6 level increased up to 100–150 times higher immediately after the race compared to the pre-race level. The source of IL-6 was not white blood cells and was not related to exercise-induced damage, but mainly produced in the working muscles.	Myokines
Pedersen et al. (2001)[13]	Current opinion in hematology; Article	Exercise and interleukin-6	The mechanism of IL-6 secretion from working muscle was reviewed, and it was suggested that the increase in muscle-derived IL-6 may be significantly associated with chronic diseases such as obesity and dyslipidemia.	Myokines
Narkar et al. (2008)[14]	Cell; Article	AMPK and PPARδ agonists are exercise mimetics	The study found that AMPK and PPAR-δ signaling interact with each other, inducing many exercise adaptations in skeletal muscle. Even sedentary mice, when treated with AICAR alone for 4 weeks, showed an upregulation of several protein genes involved in oxidative metabolism and a 44 % increase in running endurance. AMPK-PPAR-δ was reported for the first time as a targeted pathway for oral drug administration to enhance exercise adaptation and even increase endurance without exercise. AMPK and PPAR-δ considered crucial candidate molecules for exercise mimetics.	Signaling pathways
Bostrom et al. (2012)[15]	Nature; Article	A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis	For the first time, a PGC1-α-dependent myokine called irisin was discovered and its function was verified. Exercise induces the secretion of irisin, which acts on white adipose tissue, stimulating the expression of UCP1 and the development of brown fat-like tissue.	small molecular targets
Ruas et al. (2012)[16]	Cell metabolism; Article	A PGC-1α isoform induced by resistance training regulates skeletal muscle hypertrophy	The PGC-1α4, which is strongly expressed in working muscles. In a skeletal muscle-specific PGC-1α4 overexpression mouse model, it was found that specific induction of IGF-1 and suppression of myostatin could effectively resist cancer cachexia-induced muscle wasting, while significantly increasing muscle mass and strength. This suggests that PGC-1α4 is an important regulatory factor in the modulation of skeletal muscle mass and strength.	small molecular targets
Fan et al. (2013)[17]	Journal of molecular endocrinology; Review	Road to exercise mimetics: targeting nuclear receptors in skeletal muscle	Nuclear receptors and their co-regulators play a key role in regulating skeletal muscle energy metabolism and exercise-induced muscle remodeling. This review provides an overview of the collaborative role of nuclear receptors in skeletal muscle oxidative metabolism and summarizes the latest advances in exercise mimetics targeting nuclear receptors and their co-regulators.	
(Li et al., 2015)[18]	Trends in pharmacological sciences; Review	Exercise Pills: At the Starting Line	This article introduces the concept of "exercise pills" and how they simulate the effects produced by physical exercise. It provides an overview of the biological effects of "exercise pills," including the transformation of oxidative muscle fiber types, mitochondrial biogenesis, increased fat oxidation, vascular generation, and improved exercise capacity. The article also compares the beneficial effects and molecular mechanisms of sports and candidate exercise drugs.	Review of candidate exercise mimetics
Wall et al. (2016)[19]	Journal of molecular endocrinology; Review	Nuclear receptors and AMPK: can exercise mimetics cure diabetes?	This review summarizes the nuclear receptors and co-regulators that are potential targets for exercise mimetics and evaluates their therapeutic effects on diabetes.	small molecular targets
Whitham et al. (2016)[20]	Nature reviews. Drug discovery; Review	The ever-expanding myokinome: discovery challenges and therapeutic implications	The concept of "myokinome" is proposed, and substances that have been discovered and may serve as candidate exercise mimetics are summarized and classified. Techniques for discovering myokines, such as omics technologies, mass spectrometry, and proteomics, are introduced. The target of myokine therapy is elucidated, as are the current challenges of myokinome discovery.	Myokines
Fan et al. (2017)[21]	Cell metabolism; Review	Exercise Mimetics: Impact on Health and Performance	Exercise mimetics are an alternative therapy for intervening in the decline of health caused by sedentary behavior, while further exploring the scope of application for existing exercise mimetics such as GW501516 and AICAR.	Signaling pathways/ ASEM
Findeisen et al. (2019)[10]	Nature; Article	Treatment of type 2 diabetes with the designer cytokine IC7Fc	The concept of exercise mimetics was first truly designed and put into practice for the treatment of T2DM. IL-6 and CNTF were found to regulate metabolic homeostasis, but their therapeutic effects on T2DM were not satisfactory. Therefore, the gp130 binding site on IL-6 was replaced by CNTF and then combined with immunoglobulin G to remove harmful groups and retain effective groups, forming	ASEM

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Table 1 (*continued*)

Author/Year	Journal/Article type	Article	Research results	Target
			IC7Fc. It can effectively treat T2DM, prevent fat accumulation in the liver, and has minimal side effects.	
Sanford et al. (2020)[22]	Cell; Article	Molecular Transducers of Physical Activity Consortium (MoTrPAC): Mapping the Dynamic Responses to Exercise	Propose that there are still errors in determining the detailed molecular signaling underlying the beneficial health effects and disease prevention induced by exercise, but establishing a molecular atlas and database of exercise and utilizing multi-omics analysis can greatly promote addressing this issue and treating diseases.	Signaling pathways
Contrepois et al. (2020)[23]	Cell; Article	Molecular Choreography of Acute Exercise;	This project explores a multimodal and multiomics approach to investigate changes in the metabolome, lipidome, immunome, proteome, transcriptome, and microbiome during maximal oxygen uptake testing, providing new insights for the development of exercise mimetics.	Research ideas of multimethology
Gubert et al. (2021)[7]	Nature reviews. Drug discovery; Review	Exercise mimetics: harnessing the therapeutic effects of physical activity	Proposing the new concept of exercise mimetics, and advocating for it to become a new class of therapeutic intervention with a particular focus on its impact on enhancing brain function and cognition, especially in the field of central nervous system diseases.	The concept of exercise mimetics
Iwabu et al. (2021)[24]	Communications biology; Article	AdipoR agonist increases insulin sensitivity and exercise endurance in AdipoR-humanized mice	The adiponectin derived from adipocytes has been shown to activate the AMPK/SIRT1/PGC-1α pathway in skeletal muscle through its receptor AdipoR1, and increase insulin sensitivity and exercise endurance in obese diabetic mice. Therefore, the AdipoR1 signal of adiponectin is considered an important signal for exercise mimetics.	Signaling pathways
Fasipe et al. (2021)[25]	Sports Medicine and Health Science; Review	Harnessing the cardiovascular benefits of exercise: Are Nrf2 activators useful?	Exercise promotes adaptive responses by activating Nrf2, thereby improving cardiovascular health, suppressing pathological cardiac remodeling, and alleviating hypertension. Additionally, Nrf2 can be activated through pharmacological means, providing new avenues for the design of exercise mimetics.	small molecular targets
Drake et al. (2021)[26]	Proceedings of the National Academy of Sciences of USA; Article	Mitochondria-localized AMPK responds to local energetics and contributes to exercise and energetic stress-induced mitophagy	In both mouse and human skeletal muscle, an energy sensor called "mitoAMPK" exists, and metformin activates mitoAMPK in skeletal muscle without activating AMPK in other parts of the cell. This suggests the importance of mitoAMPK in the treatment of chronic diseases. The team also developed an effective gene model to predict the key steps of mitoAMPK activation, which can be used to promote regular exercise, prevent diseases, and develop effective exercise mimetics.	Signaling pathways
Correia et al. (2021)[27]	Cell metabolism; Article	Muscle-secreted neurturin couples myofiber oxidative metabolism and slow motor neuron identity	After eight weeks of rotating exercise, the expression of the neurotrophic factor NRTN in mouse skeletal muscles was found to be elevated along with PGC-1. Additionally, the mRNA of NRTN in the gastrocnemius muscle of rats and humans increased significantly after exercise. A transgenic mouse model overexpressing NRTN (HSA-NRTN) was constructed, and the results showed that HSA-NRTN not only plays a key role in improving neuromuscular junctions, maintaining muscle fiber structure, and regulating local energy metabolism but also significantly improves mouse endurance and speed, as well as slowing down the degenerative disease of motor neurons.	Signaling pathways
De Miguel et al. (2021)[28]	Nature; Article	Exercise plasma boosts memory and dampens brain inflammation via clusterin	The study for the first time transferred plasma from active individuals to sedentary individuals in vitro and found that one of the important mechanisms by which exercise improves neurodegenerative diseases is that exercise can produce clusterin, a protein that reduces baseline expression of neuroinflammatory genes and experimentally induced brain inflammation, and has a significant therapeutic effect on neurodegenerative diseases.	small molecular targets
Leiter et al. (2022)[29]	Cell metabolism; Article	Selenium mediates exercise-induced adult neurogenesis and reverses learning deficits induced by hippocampal injury and aging	Treadmill exercise significantly upregulates the expression of SEPP1 in mice and promotes the proliferation of NPC and the potential for neuronal lineage differentiation in the hippocampus, without affecting cell apoptosis. Animal cognitive function tests have found that exogenous selenium supplementation can significantly improve mice's hippocampus-dependent spatial learning and memory abilities, indicating that selenium may be a key substance for restoring age-related hippocampal functional defects and effectively reversing hippocampal injury-related cognitive decline. These findings provide new ideas for developing exercise mimetics.	small molecular targets
Li et al. (2022)[30]	Nature; Article	An exercise-inducible metabolite that suppresses feeding and obesity	After treadmill exercise, the small molecule metabolite Lac-Phe significantly increased in the plasma of mice and horses. Lac-Phe is synthesized by CNDP2 through the condensation of lactate and phenylalanine. Lac-Phe can	small molecular targets

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Table 1 (*continued*)

Author/Year	Journal/Article type	Article	Research results	Target
Kurz et al. (2022)[11]	Cancer Cell; Article	Exercise-induced engagement of the IL-15/IL-15Rα axis promotes anti-tumor immunity in pancreatic cancer	effectively inhibit the food intake of mice, improve glucose homeostasis, reduce fat mass and body weight, and prevent obesity. Human studies have found that the level of Lac-Phe in the plasma continues to increase after exercise, and it is one of the key metabolites regulating human exercise. Aerobic exercise can increase adrenaline secretion and upregulate the expression of $CD8^+$ T cells and IL-15Rα, which are sensitive to IL-15, thereby leading to the accumulation of $CD8^+$ T cells and IL-15Rα on pancreatic cancer cells and ultimately killing the tumor cells and inhibiting the development of pancreatic cancer. Based on this mechanism, Novartis has developed an IL-15 agonist called NIZ985, which can mimic the effect of exercise in enhancing the IL-15/IL-15Rα signaling pathway, reduce potential inflammatory reactions, and achieve sustained anti-tumor effects.	ASEM

Note. UCP1, uncoupling protein 1; PGC-1α4, PGC-1 gene encodes a protein; IGF-1, insulin-like growth factor-1; T2DM, type 2 diabetes; AMPK, AMP-activated protein kinase; SEPP1, selenium protein P; NPC, neural progenitor cells; Lac-Phe, N-lactoyl-phenylalanine; CNDP2, cytosolic non-specific dipeptidase 2; IL-15, interleukin 15; ASEM, Artificially synthesized exercise mimetics.

diseases.[30] Therefore, signaling pathways and small molecular targets related to skeletal muscles and exercise mimetics have been extensively studied, and may provide new insights and strategies for the development of exercise mimetics as pharmacological interventions for various health conditions.

2.3. Artificially synthesized exercise mimetics

In October 2019, Mark Febbraio of Gavin Institute of Medicine, Sydney, Australia reported in Nature a method for artificially synthesizing exercise mimetics and designed a small molecule compound, IC7Fc,[10] which has therapeutic effects on type 2 diabetes. This provides a new strategy for exercise mimetics in the field of metabolic disease treatment. In July 2022, Professor Dafna Bar-Sagi of Grossman Medical College of new york University reported the anti-tumor effect of exercise in Cancer Cell and developed exercise mimetics. Research has revealed that the IL-15 agonist NIZ985 can simulate exercise-enhanced IL-15/IL-15Rα signaling pathways, thereby promoting the destruction of tumor cells.[11] This presents a novel avenue for the application of exercise mimetics in the field of cancer therapy.

It should be pointed out that in the field of exercise mimetics research, breakthroughs and explorations are still ongoing. It is urgent to promote the development of exercise mimetics through the interdisciplinary integration of sports science, pharmacy, and other fields.

3. The relationship between exercise mimetics and exercise

Exercise mimetics use the health benefits produced by exercise as a source of drug design to seek potential new methods for disease treatment. This method of treatment, which simulates or enhances the therapeutic effects or health benefits of exercise, is known as exercise mimetics. In recent years, exercise mimetics have gradually emerged as a research focal point. The changing lifestyles and working habits of individuals have resulted in a lack of physical activity and an increase in sedentary behavior. Consequently, a global estimate indicates that 31.1 % of adults fail to meet the minimum recommended exercise standards for maintaining health.[41] This indirectly leads to a dramatic increase in the incidence of "modern civilization diseases" (including obesity, type 2 diabetes,[42] and cardiovascular disease, etc.[43]). Appropriate exercise training is one of the important means to prevent and treat these diseases, Including moderate-intensity aerobic training,[44] high-intensity aerobic training,[45] and lower limb resistance training.[46] For example, adults with type 2 diabetes and metabolic syndrome who underwent three months of aerobic exercise training and high-intensity exercise training observed a decrease in insulin resistance and systemic inflammation markers, which appeared to be related to an increase in peak oxygen uptake rather than weight loss.[47] Furthermore, during exercise, immune cells in the tumor infiltrate in large numbers, leading to a reduction of over 60 % in the incidence and growth of tumors in several mouse models, as well as the prevention of tumor or cancer-related death.[48] Exercise training is also an effective method for treating most neurological disorders.[49] By injecting circulating blood factors from mice after exercise into sedentary mice, baseline neuroinflammatory gene expression and experimentally induced brain inflammation can be reduced, and cognitive function can be improved.[28]

Considering the insufficient amount of human exercise prescriptions and the human and economic burden caused by these diseases, and taking into account the health benefits of exercise, including neurological and psychiatric disorders,[50,51] cardiovascular diseases,[52] metabolism and inflammation,[53] and tumors,[54] the academic community has gradually focused on alternative therapies using exercise mimetics.[55] Exercise mimetics are closely related to human physical activity. Different types and intensities of exercise have different health benefits. In theory, the greater the intensity of exercise, the more significant the improvement in various aspects of heart rate, metabolism, and physiological function.[56,57] In addition, different genetic characteristics, environments, cells, molecules, or system levels of individuals can also lead to differences in the exercise benefits produced by different types of exercise (aerobic or resistance), including improvement or inhibition of organismal health benefits.[58–60] Based on the design concept of exercise mimetics, this study will focus on known forms of exercise that can produce therapeutic effects, and summarize and determine the exercise molecular targets that are related to therapeutic effects as effective sources of exercise mimetic molecules.

It is worth noting that although exercise mimetics may not be able to fully mimic the wide range of benefits of exercise, the emerging candidate exercise mimetics[14,61,62] are a favorable potential choice for people who cannot exercise regularly due to obesity, amputation, spinal cord injury, metabolic diseases, and musculoskeletal or cardiovascular diseases. The design concept of these exercise mimetics is to activate signal molecules related to exercise, which are logically considered to be effective pharmacological targets for such exercise mimetics.[7,63,64] Therefore, the development of exercise mimetics is feasible.

4. Candidate molecular sources of exercise mimetics

The human body is a highly complex system that maintains homeostasis through dynamic interactions among multiple levels of entities, ranging from cells, tissues, organs to systems, through various means such as neural, endocrine and exocrine pathways. Exercise, as an

external stimulus, can disrupt and modulate this complex system, and appropriate exercise can have beneficial effects on human health. These changes include the metabolic, proteomic, genomic, immunological, and gut microbiota profiles, which can serve as potential sources of exercise mimetics. Exercise mimetics can be roughly classified into nine categories based on their sources and effects (Fig. 1).

① Neurotrophins, such as brain-derived neurotrophic factor (BDNF). Exercise can upregulate BDNF expression, which plays a critical role in neuronal survival, proliferation, maturation, and growth in the brain (including the hippocampus, hypothalamus, and cortex).[65] Clinical studies have found that BDNF has a positive therapeutic effect on clinical models of Alzheimer's disease (AD), Huntington's disease (HD), and other brain disorders.[20,66,67] It is worth noting that BDNF is not only produced in the brain but also observed to increase in skeletal muscles after exercise.[68] Further research has confirmed that exercise can upregulate BDNF in skeletal muscles and participate in exercise-induced muscle regeneration.[69] In addition, BDNF can also affect tissue metabolism via autocrine or paracrine signaling, including fat oxidation,[70] insulin resistance, and playing a crucial role in angiogenesis, cardiovascular development, and cardiac protection.[71]

② Neurotransmitters and neuropeptides, including glutamate (GLU), serotonin (5-HT), and neuropeptide Y (NPY). Exercise can regulate the level of GLU,[72] which can stimulate the production of BDNF as a neurotransmitter, thereby changing the sensitivity of neurons to GLU and Ca2+ stability and ultimately changing the plasticity of neurons.[73] 5-HT is an important neurotransmitter for exercise-induced adult neurogenesis[74] and a key factor in hippocampal neurogenesis.[75] In addition, exercise can upregulate the plasma NPY level in the rat hypothalamus,[76] which is closely related to increased anxiety, cognitive impairment, and changes in hippocampal synaptic plasticity.[77]

③ Intestinal flora and their metabolites, such as the phylum Firmicutes and short-chain fatty acids (SCFA), etc. With the development of related technologies such as genomics and bioinformatics, the relationship between fecal intestinal flora and their metabolites and health has gradually been discovered. Exercise can change the composition and abundance of intestinal flora, and then improve overall gut health and promote organismal health.[78–80] In addition, the intestinal flora has a bidirectional communication with various organs and tissues of the body, such as the cardiovascular system (gut-heart axis), the immune system (gut-immune axis), the skeletal muscle (gut--muscle axis), and the brain (gut-brain axis),[81] making it a potential target for disease treatment.

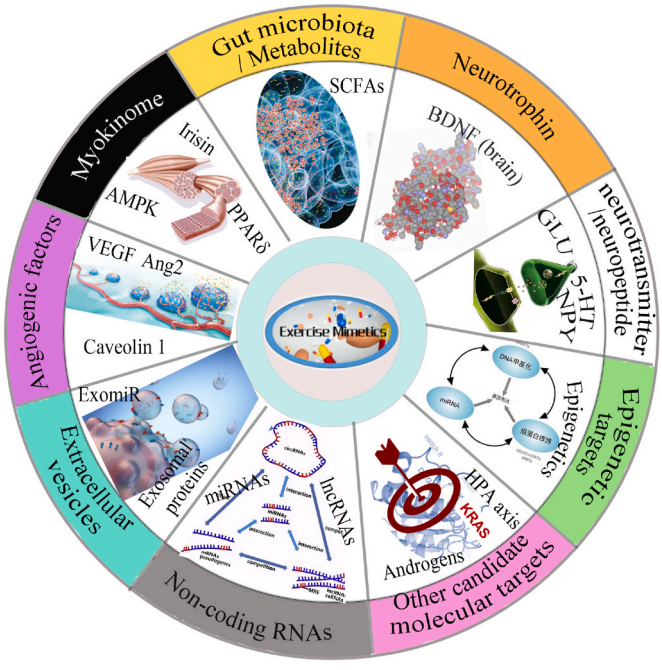

Fig. 1. Molecular mediators and drug-making targets of exercise mimetics.

④ Myokines, including AMPK or PPAR agonists such as AICAR and GW501516, muscle-derived neurotrophic factors (BDNF (muscle)), as well as myokines such as irisin, insulin-like growth factor 1 (IGF1), and cathepsin B. Exercise can induce skeletal muscle remodeling and related metabolic pathways through the AMPK-sirtuin 1 (SIRT1)-PPARδ pathway, which is crucial for muscle energy metabolism and mitochondrial biogenesis, and is one of the main targets for developing exercise mimetics.[21,82] AICAR and GW501516 (a selective PPARδ agonist) have been shown to indirectly improve memory function and neurogenesis (possibly through the IL-6-mediated increase in BDNF[83] and cathepsin B[84]).[85] In addition, metformin (targeting AMPK) has a positive effect on cognitive function in an Alzheimer's disease mouse model.[86] These are potential molecules for developing exercise mimetics.

⑤ Vascular growth factors, exercise-induced increases in vascular endothelial growth factor (VEGF), VEGFR2, Ang2, and $CD34^+$ cells (vascular generation markers) can effectively prevent the occurrence and development of stroke and related diseases.[87] In addition, studies have found that the use of SU1498 (a VEGF receptor FLK1 inhibitor) prevents exercise-induced improvement of depression-like behavior, indicating that VEGF is a key factor in the exercise anti-depression effect.[88] Moreover, VEGF is also a key substance for exercise-induced adult hippocampal neurogenesis.[89] Moreover, recent advancements in research suggest that exercise triggers adaptive alterations in early lymphatic behavior, inducing an upregulation of lymphangiogenesis. Key regulatory factors in muscle lymphangiogenesis include vascular endothelial growth factor receptor-3 (VEGFR-3) and its ligands, VEGF-C and VEGF-D.[90] Notably, recent investigations emphasize the involvement of lymphangiogenesis in exercise-induced physiological cardiac hypertrophy. This process entails the elevation of VEGFR3 levels through exercise, and the initiation of cardiac lymphangiogenesis requires the activation of VEGFR3.[91] Additionally, a growing body of evidence highlights the role of lymphangiogenesis in tissue repair and regeneration.[92] In summary, this underscores the potential contributions of lymphangiogenesis and its associated receptor proteins in facilitating tissue recovery and regeneration through exercise. Consequently, lymphangiogenesis and its related secretory receptor proteins emerge as promising therapeutic targets.

⑥ Extracellular vesicles, which refer to molecular structures that can contain and transport biological materials (including DNA, RNA, proteins, and lipid molecules) between cells, are connecting tissues throughout the body.[93] The number of extracellular vesicles in circulation increases 2–4 times after exercise, which is considered one of the important pathways for inter-tissue signaling during exercise and has positive promoting effects on health.[94,95]

⑦ Non-coding RNA, such as microRNAs (miRNAs). Exercise can regulate the expression of miRNAs.[96] miRNAs are the most extensively studied type of non-coding RNA among small non-coding RNAs (sncRNAs) and can act as "master regulators" by regulating gene expression,[97] with positive therapeutic effects.[98] It has also been shown that long non-coding RNA (lncRNA) is responsive to physical exercise.[99] lncRNAs play a crucial role in regulating signaling pathways associated with DNA, mRNA, and protein, thereby influencing gene expression in

various biological and pathophysiological contexts, such as neuronal disorders, immune responses, and cancer.[100] Consequently, lncRNAs hold immense therapeutic potential.

⑧ Epigenetic targets mainly refer to epigenetic modifications, including DNA modifications (such as DNA methylation), histone modifications, and non-coding RNA (as mentioned above). DNA modifications (such as DNA methylation) can provide specific molecular targets for various therapeutic methods, including epigenetic editing.[101] DNA methylation can effectively regulate cognitive function and treat neurodegenerative diseases,[102] and is also one of the potential targets for cancer treatment.[103] Histone modification can be targeted for treatment, such as histone deacetylase (HDAC) inhibitors.[104] Studies have found that exercise, cognitive stimulation, and other forms of intervention can cause epigenetic changes.[105–107] In addition, promoting histone acetylation transferase (HAT) activity or inhibiting histone deacetylase (HDAC) activity can promote histone acetylation, thereby activating chromatin, promoting gene expression and translation, and participating in the regulation of immune function,[108] cardiovascular function,[109] and nervous system function.[110]

⑨ Other molecular targets, such as androgens, have been found to be upregulated by exercise, promoting protein synthesis, skeletal muscle metabolism, and red blood cell production to promote overall health.[111] In addition, androgens can also mediate exercise-induced neurogenesis and synaptic plasticity. It can be seen that androgens are a key substance in promoting health through exercise and a potential molecular target for exercise mimetics. Moreover, mitochondrial biogenesis[112] and glucose uptake[113] and other molecular processes are also considered potential targets for exercise mimetics, and further research is needed to explore the feasibility of drug development.

5. Targeting system for exercise mimetics

5.1. Skeletal system

The main target system of the exercise mimetics substance is the skeletal system, and applying the exercise mimetics substance to solve physiological problems related to bones and skeletal muscles is currently the most researched and promising direction. The primary mechanism and principle of its action are shown in Fig. 2.

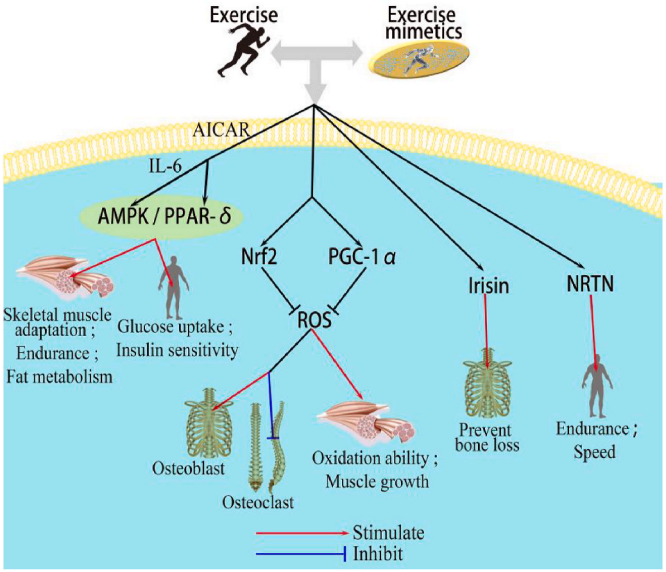

Fig. 2. Schematic diagram of exercise mimetics regulating skeletal system.

As early as 2008, Narkar discovered that AMPK and PPAR-δ could improve metabolic characteristics and endurance even in sedentary mice when studying substances with exercise mimetics properties.[114] Subsequent research also confirmed that the main features of the exercise mimetics substance are mostly focused on promoting the physiological health adaptation of skeletal muscles, which may be due to the fact that the working and target systems of exercise training are both the skeletal system, which leads to metabolic adaptations in skeletal muscles and extensive physiological effects caused by the release of metabolites and myokines, making it an important reason for promoting the health and function of the skeletal system and other organ systems.[21] AICAR and IL-6 are effective activators of AMPK and PPAR-δ. AICAR effectively enhances the adaptive and endurance qualities of exercise-induced skeletal muscles by activating the AMPK and PPAR-δ signaling pathways.[14] IL-6 enhances glucose uptake and insulin sensitivity of the body by activating AMPK, and increases fatty acid metabolism in vitro skeletal muscles.[12] Therefore, AMPK and PPAR-δ are one of the important candidate molecules for exercise mimetics substances.

Nrf2 and PGC-1α may also be one of the candidate exercise mimetics for the musculoskeletal system. It is well-known that intense or excessive exercise can lead to excessive production of reactive oxygen species (ROS) and damage to the antioxidant defense system in skeletal muscle.[115] Nrf2 is a regulatory factor for oxidative stress, and both its own regulation and its regulation of oxidative stress are involved in bone metabolism. Nrf2 agonists have a protective effect on the survival of osteoblasts (including osteoblasts, bone cells, and stem cells) and can directly inhibit osteoclast differentiation by resisting oxidative stress.[116] In addition, several synthetic and natural compounds can also regulate Nrf2 activity, and various Nrf2-based drugs have begun to be applied in the treatment of bone and muscle diseases.[117] Since the main function of exercise mimetics also includes reducing oxidative stress, Nrf2 may be a new method for the treatment of bone and muscle diseases.

It is worth noting that the oxidative stress generated during skeletal muscle adaptation to exercise is mainly mediated by the recruitment of PGC-1α. PGC-1α can maintain mitochondrial function and integrity, and then adapt to exercise-induced oxidative stress.[118] Currently, PGC-1α agonists have begun to be studied.[119] In addition, metabolic regulators can also affect PGC-1α, increase the oxidative capacity of skeletal muscle, and stimulate myogenic genes in elderly mice.[120] In addition, Irisin and NRTN may also be potential exercise mimetics. Irisin is closely related to bone health,[121] and the use of irisin can improve bone formation and fracture recovery, prevent cell death and disuse-induced bone loss induced by dexamethasone.[122] Exercise can also upregulate the expression of NRTN in working muscles, and overexpression of NRTN can significantly improve endurance and speed in mice, as well as slow down the degenerative changes of motor neurons.[27] These key factors in the musculoskeletal system may serve as candidate targets for exercise mimetics to achieve the effect of promoting health through exercise.

5.2. Endocrine system

The endocrine system is also one of the target systems for exercise mimetics. Applying exercise mimetics to solve metabolic problems in the body, especially diabetes, is one of the key research targets of exercise mimetics. Its main mechanism of action is shown in Fig. 3.

Differing from PPAR-α, PPAR-δ predominantly regulates skeletal muscle, while PPAR-α primarily governs the gene expression related to oxidative metabolism and lipid balance, and lipid balance and plays a role in adapting to metabolic homeostasis in the liver.[123] It is worth noting that PPAR-α has several known endogenous ligands, such as fatty acids,[124] and the fasting response (caloric restriction) also releases fatty acids that activate PPAR-α.[125] Therefore, the candidacy of PPAR-α as an exercise mimetic is still controversial. Based on this, researchers have proposed a new candidate, the endocrine hormone fibroblast growth factor 21 (FGF21), which is produced and secreted by the liver in

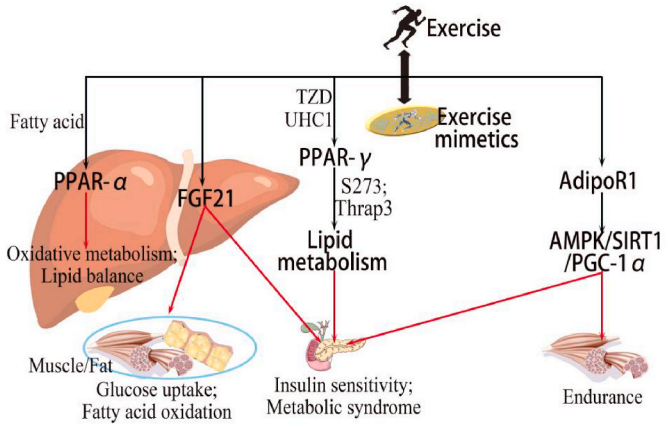

Fig. 3. Schematic diagram of exercise mimetics regulating endocrine system.

response to metabolic disorders caused by fasting response, etc.[126,127] Intense exercise can induce FGF21 expression and increase FGF21 levels in circulation.[128] In addition, FGF21 can stimulate glucose uptake and fatty acid oxidation in metabolic tissues such as muscle and fat, effectively preventing the body from entering a state of hunger.[129,130] Animal experiments have also confirmed that in FGF21 overexpression mouse models, high doses of FGF21 significantly improved insulin sensitivity and resistance to metabolic syndrome.[131] This suggests that FGF21 could be a potential candidate exercise mimetic for improving metabolic diseases. In the future, the focus should be on exploring the normal physiological metabolic response induced by FGF21 production (not caused by intense exercise or high-intensity exercise) or researching corresponding effective activators; at the same time, the activation process of PPAR-α should be avoided (should not be produced by hunger), and corresponding blocking methods should be studied.

PPAR-γ is also one of the important targets for treating metabolic diseases. PPAR-γ plays a crucial role in the development of adipose tissue by regulating the expression of lipid metabolism genes and adipokines with key metabolic functions, such as adiponectin132. There are many factors that influence PPAR-γ activity and the expression of target genes in adipose tissue, including exercise and other stressors, suggesting that PPAR-γ is a potential target for the development of novel exercise mimetics.[133] Thiazolidinediones (TZDs) are a classic class of drugs that activate PPAR-γ and counteract diabetes.[134] TZDs enhance the development and lipid handling of adipocytes by activating PPAR-γ, increasing the uptake of circulating fatty acids into adipose tissue, and reduce insulin resistance.[135] Recent studies have found that TZDs inhibit the phosphorylation of the S273 residue of PPAR-γ by cyclin-dependent kinase 5 (CDK5), resulting in changes in the expression pattern of PPAR-γ target genes in white adipose tissue, which may be a potential factor preventing obesity.[136] Phosphorylation of S273 can bind to thyroid hormone receptor-associated protein 3 (Thrap3), which is crucial for PPAR-γ activity in obesity.[137] Unlike TZD agonist drugs, studies have found that non-agonist PPAR-γ ligands (UHC1) effectively block the S273 phosphorylation of PPAR-γ and improve insulin sensitivity and diet-induced obesity in the treatment of T2D.[138] These studies suggest that PPAR-γ can be used as a therapeutic target for diabetes (with Thrap3 and CDK5 as key influencing factors) and as a candidate molecule for exercise mimetics.

In addition, the adiponectin receptor AdipoR1 signaling pathway is considered an important signal for exercise mimetics. Studies have found that in AdipoR1 gene knockout mouse models, the use of AdipoR agonists (AdipoRon) can exert beneficial effects through AdipoR in muscles, increasing insulin sensitivity and exercise endurance in AdipoR mice.[24] This suggests that adiponectin from adipocytes displays its beneficial effects in skeletal muscles through its receptor AdipoR1, activating AMPK/SIRT1/PGC-1α, and increasing insulin sensitivity and exercise endurance in obese diabetic mice.[24] Adiponectin and its receptor can be potential exercise mimetic molecules for treating metabolic diseases.

5.3. Circulatory system

The circulatory system, especially the cardiovascular system, is also one of the future research directions of exercise mimetics materials. Its main mechanism is shown in Fig. 4.

The IGF1/PI3K/AKT signaling pathway is a key mechanism in exercise-induced physiological myocardial hypertrophy and cardiac protection. Exercise induces the secretion of IGF1, activates IGF1R tyrosine kinase (TK),[139,140] and recruits PI3K.[141] PI3K further converts PIP2 to PIP3 in the plasma membrane,[142] which recruits PDK1 and AKT to the plasma membrane and then activates and phosphorylates PDK1 and AKT,[143] which is the IGF1/PI3K/AKT signaling pathway. Activation of this pathway can effectively promote myocardial cell contraction, which is crucial in regulating exercise-induced physiological myocardial hypertrophy. It plays a protective role in the heart by promoting myocardial cell contraction, improving survival rate, reducing myocardial cell apoptosis, inhibiting pathological hypertrophy, promoting angiogenesis, and so on.[144–146]

Noncoding RNAs also play an important role in the cardiovascular system. Exercise upregulates miR-222 and LncRNA CPhar in the heart, while downregulating lncExACT1.[147] LncRNA CPhar binds to DDX17, sequestering C/EBPβ and thereby inhibiting ATF7 transcription.[148] Additionally, LncExACT1 can bind to miR-222, and exercise downregulates LncExACT1, leading to the release of more miR-222, which helps to induce exercise-induced physiological cardiac hypertrophy.[149] LncExACT1 also actively regulates the most similar protein-coding gene, DCHS2, and reduces LncExACT1 activation of Yes-associated protein (YAP).[148] These noncoding RNAs are involved in regulating exercise-induced physiological cardiac hypertrophy and have a protective effect on myocardial injury and pathological cardiac hypertrophy.[150] Furthermore, exercise can regulate miR-34a and miR-126, inducing endothelial cell-derived small extracellular vesicles (sEVs) containing miR-342–5p and cardiac sEVs derived from brown adipose tissue containing miR-125b-5p, miR-128–3p, and miR-30d-5p to

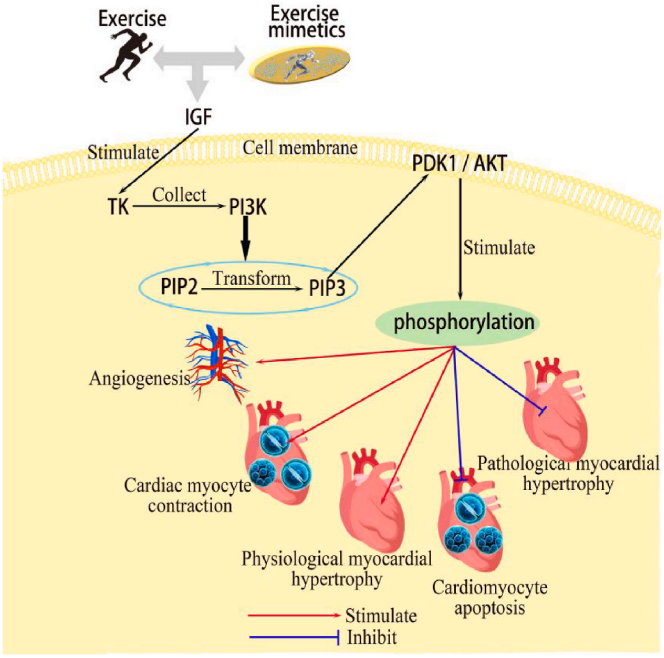

Fig. 4. Schematic diagram of the effects of exercise mimetics on the regulation of the circulatory system.

prevent myocardial injury and cardiac remodeling.[151] These findings suggest that the IGF1/PI3K/AKT signaling pathway and noncoding RNAs and their regulatory signaling pathways can serve as potential targets for exercise mimetics, as well as potential molecular targets for treating cardiovascular diseases.

5.4. Neurological system

The neurological system is currently a hot research topic in the field of exercise mimetics. The main mechanism of its action is shown in Fig. 5.

Another key target system for exercise mimetics is the neurological system, which enhances neuronal plasticity, particularly in adult neurogenesis and synaptic plasticity, improving cognitive function and preventing the occurrence of neurological disorders.[51,82] Different molecular processes and signaling pathways are associated with the enhancement of adult neurogenesis and synaptic activity after exercise, including signal transduction pathways such as BDNF, tyrosine receptor kinase B (TrkB), glutamatergic, dopaminergic, and adrenergic systems.[77,152–155] In addition, at the cellular level, the effects of exercise on glial generation, neurogenesis, synaptic genesis, and angiogenesis lead to structural and functional changes, ultimately enhancing brain function, including cognition.[156] Studies have found that exercise can increase the volume of the hippocampal dentate gyrus/CA3 and enhance memory in young people[157] Furthermore, extensive evidence supports the enhancement of adult neurogenesis and synaptic plasticity induced by exercise.[158–160] Exercise has also been shown to reverse learning deficits caused by hippocampal injury by promoting adult neurogenesis.[161] It is evident that exercise is one of the important factors that affect the neurological system. The main pathways by which exercise affects the neurological system include: (1) exercise can affect molecules such as BDNF, neurotransmitters, neuropeptides, and non-coding RNAs, promoting adult neurogenesis and enhancing hippocampal synaptic plasticity[7]; (2) exercise can induce the expression of clusterin and selenoprotein P (SEPP1). Clusterin can reduce baseline expression of inflammatory genes and experimentally induced brain inflammation, thus preventing the occurrence of neurodegenerative diseases.[28] SEPP1 can promote proliferation of hippocampal NPCs and their neuronal lineage potential, effectively reversing cognitive decline related to hippocampal injury.[29] These findings suggest that exercise mimetics can mimic the expression of brain-derived substances or induce the generation of certain key factors, thereby enhancing the neuroprotective effect and improving brain function.

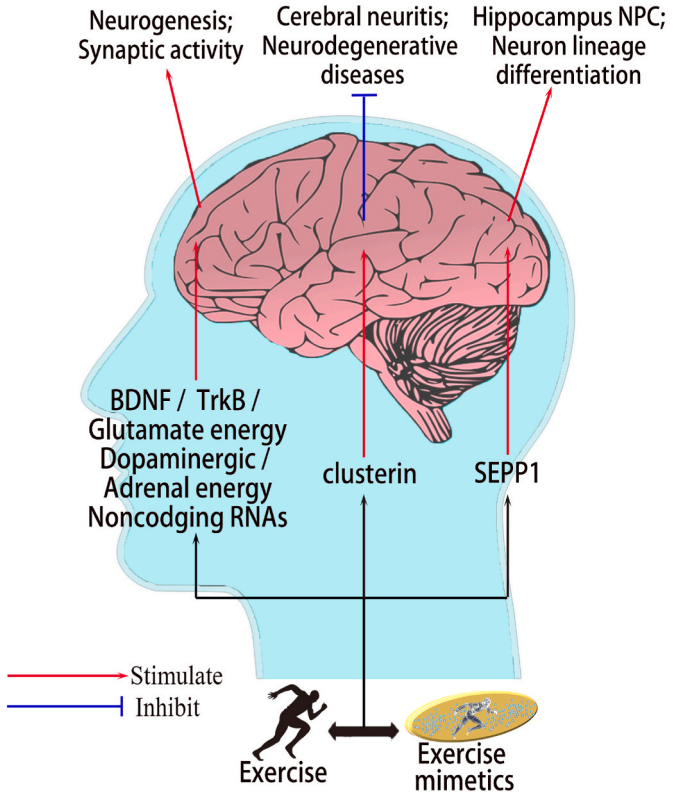

Fig. 5. Schematic diagram of effects of exercise mimetics on brain structure and function.

5.5. Other targeted organs and functions of exercise mimetics

There has been less research on exercise mimetics in other systems of the human body, such as the reproductive, respiratory, digestive, and urinary systems. The immune system is a promising molecular target for exercise mimetics, and may play a role in cancer treatment. It is well known that the mechanism of cancer development is complex, involving multi-factorial and multi-step reactive processes that are closely related to lifestyle, environment, genetics, and other factors. Treatment is difficult, and the main diagnostic and therapeutic methods currently available are drug therapy and surgery.[162] However, with the development of exercise science and drug research, scientists have discovered that exercise is a potential approach for cancer treatment. For example, the IL-15 agonist NIZ985 has demonstrated the ability to mimic the effects of exercise by enhancing the IL-15/IL-15Rα signaling pathway, leading to the inhibition of pancreatic cancer.[11] NIZ985 may become a new exercise mimetic for cancer treatment. This suggests that exercise mimetics are likely to be one of the potential directions for cancer treatment, and in the future, more exercise targets for the treatment of other cancers need to be explored, providing new directions for cancer treatment.

6. Future research trends of exercise mimetics

Exercise mimetics have enormous potential for the prevention and treatment of human diseases. However, the current number of developed and utilized exercise mimetics is extremely limited, due to the complex physiological, metabolic, and endocrine changes and adaptations that occur during exercise. It is difficult for a single exercise mimetic to summarize all such systemic changes. However, it should be noted that exercise mimetics only need to mimic or enhance a subset of therapeutic effects of exercise to have clinical impact, which is the main research goal of current exercise mimetics. In addition, the development of exercise mimetics requires a deeper understanding of the molecular and cellular mechanisms of beneficial therapeutic effects induced by exercise, including changes at the molecular, cellular, tissue, organ, and systemic levels. However, understanding this mechanism is challenging, as exercise itself directly or indirectly affects changes at various levels of the body.[163] Despite the difficulty in elucidating this complex mechanism of action, current research on exercise mimetics has enabled us to begin utilizing some of their therapeutic potential.[164]

Possible research directions in the future include utilizing interdisciplinary technologies such as bioinformatics and artificial intelligence to investigate the characteristics of existing motion simulation agents. These studies can help identify common structures of potential artificial motion simulation agents. For example, Alphafold2 is a technique used to predict the key conformational changes of drug aggregation and the associated protein subunits, enabling precise prediction of the three-dimensional structural features of drugs.[165] There are many applications of artificial intelligence in the field of medicine, including: 1) Identification of Biomarkers or Biological Targets: AI accelerates the screening process of candidate molecules for exercise mimetics by simulating their structure and properties, leading to the identification of optimal candidates. 2)Simulation of Clinical Experiments and Outcome Prediction: AI, by integrating candidate exercise mimetic molecules,

simulates potential exercise mimetics, predicting their possible clinical trial results and effects, and provides prior feedback and adjustment suggestions. 3)Prediction and Monitoring of Drug Side Effects: AI analyzes medical records and drug databases to forecast potential side effects and adverse reactions associated with exercise mimetics. This capability ensures the timely detection and adjustment of safety issues related to these drugs. In general, the application of artificial intelligence in the field of medicine can greatly improve the efficiency and accuracy of drug development, enhance the success rate and effectiveness of clinical trials, help doctors make personalized treatment decisions, and ensure patient drug safety, which can also be used to guide the development of motion simulation drugs. Furthermore, motion simulation may also be applied in preventive medicine, where genomics and selective biomarker arrays can be used to identify high-risk populations who can be targeted for specific treatments to delay or prevent the onset of specific diseases. Additionally, further exploration of the targeted systems of motion simulation agents is necessary to enrich the study of the biological improvement effects of these agents.

7. Summary

Exercise mimetics are still in the early stages of research. The beneficial effects of exercise-induced cytokines and microbiota on the body have led to the development of exercise mimetics, a term that encompasses both such substances and living organisms, including new compounds synthesized through biotechnology. Exercise mimetics include small molecules, peptides, antibodies, non-coding RNA, gut microbiota, and epigenetic editing constructs, among others. Additionally, research on exercise mimetics is complementary to that on exercise itself, with the goal of using the features and functional properties of the health benefits induced by simulated exercise to design new potential methods for treating diseases. Currently, it has been found that the target systems of exercise mimetics include the exercise system, circulatory system, and nervous system, and there is likely a biological improvement effect in the immune and endocrine metabolism systems as well. In the future, the development of exercise mimetics should be aided by technologies such as bioinformatics and artificial intelligence.

Author contributions

Yuping Zhu performed the literature search and data analysis, and Gang Song drafted and critically revised the manuscript.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors agreed on the publication of the current version of manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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Abbreviations

EIM	exercise is medicine
GP130	glycoprotein 130
IL-6	interleukin 6
CNTF	ciliary neurotrophic factor
LIF	leukemia inhibitory factor
IgG	immunoglobulin G
UCP1	uncoupling protein 1
AMPK	AMP-activated protein kinase
IGF-1	insulin-like growth factor-1
SEPP1	selenium protein P-1
NPC	neural progenitor cells
Lac-Phe	N-lactoyl-phenylalanine
CNDP2	cytosolic non-specific dipeptidase 2
NRTN	neurotrophin
HSA-NRTN	human alpha-skeletal actin neurotrophin
BDNF	brain-derived neurotrophic factor
AD	Alzheimer's disease
HD	Huntington's disease
GLU	glutamate
NPY	neuropeptide Y
SCFA	short-chain fatty acids
SIRT1	sirtuin 1
VEGFs	vascular endothelial growth factors
HDAC	histone deacetylase
HAT	histone acetylation transferase
ROS	reactive oxygen species
FGF21	fibroblast growth factor 21
CDK5	cyclin-dependent kinase 5
TK	tyrosine kinase
sEVs	small extracellular vesicles
TrkB	tyrosine receptor kinase B

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