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Journal

Journal of Sport and Health Science, 9(3)

ISSN

2095-2546

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Publication Date

2020-05-01

DOI

10.1016/j.jshs.2019.09.008

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ScienceDirect

Journal of Sport and Health Science 9 (2020) 211–227

www.jshs.org.cn

Review

Impacts of exercise intervention on various diseases in rats

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Received 12 December 2018; revised 6 June 2019; accepted 6 September 2019

Available online 28 October 2019

Abstract

Background: Exercise is considered as an important intervention for treatment and prevention of several diseases, such as osteoarthritis, obesity, hypertension, and Alzheimer's disease. This review summarizes decadal exercise intervention studies with various rat models across 6 major systems to provide a better understanding of the mechanisms behind the effects that exercise brought.

Methods: PubMed was utilized as the data source. To collect research articles, we used the following terms to create the search: (exercise [Title] OR physical activity [Title] OR training [Title]) AND (rats [Title/Abstract] OR rat [Title/Abstract] OR rattus [Title/Abstract]). To best cover targeted studies, publication dates were limited to "within 11 years." The exercise intervention methods used for different diseases were sorted according to the mode, frequency, and intensity of exercise.

Results: The collected articles were categorized into studies related to 6 systems or disease types: motor system (17 articles), metabolic system (110 articles), cardiocerebral vascular system (171 articles), nervous system (71 articles), urinary system (2 articles), and cancer (21 articles). Our review found that, for different diseases, exercise intervention mostly had a positive effect. However, the most powerful effect was achieved by using a specific mode of exercise that addressed the characteristics of the disease.

Conclusion: As a model animal, rats not only provide a convenient resource for studying human diseases but also provide the possibility for exploring the molecular mechanisms of exercise intervention on diseases. This review also aims to provide exercise intervention frameworks and optimal exercise dose recommendations for further human exercise intervention research.

Key Words: Cancer; Disease; Exercise intervention; Method; Rats; System

1. Introduction

In recent years, exercise as a treatment for several diseases has attracted the attention of many researchers. Research has shown that proper exercise effectively prevents chronic noncommunicable diseases[1,2] and can also play an important role in delaying disease progression,[3,4] treating pre-existing diseases, and reducing complications and mortality due to disease.[5] However, if not properly prescribed or practiced, exercise has been shown to lead to physical health damage, including impairing the body's immune function[6] and increasing the risk of physical injury.[7] What's worse, excessive exercise may overload the circulatory system, causing acute renal failure, cardiac arrest, or even interruption of cerebral blood flow.[8,9]

For a number of reasons, rats are currently one of the most suitable animal models for human disease research. Compared to mice, rats are larger in size, have longer life spans, and offer easier collection of physiological data. Additionally, rats have stronger disease resistance and are more adaptable; thus, they are easier to breed. Rats have cognitive function that is similar to that of humans, but it is much easier for researchers to acquire enough rat models with specific diseases to study comprehensively the mechanisms of exercise on diseases. For example, Castrogiovanni et al.[10] applied the synovium of an osteoarthritis-induced rat model to determine the influence of moderate physical activity on the expression of osteoarthritis-related anti-inflammatory and chondroprotective biomarkers.

Studies have shown that the effects of exercise vary with exercise type, frequency, intensity, and rat model. It has been well established that exercise can improve the condition of

Peer review under responsibility of Shanghai University of Sport.

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https://doi.org/10.1016/j.jshs.2019.09.008

Cite this article: Wang R, Tian H, Guo D, Tian Q, Yao T, Kong X. Impacts of exercise intervention on various diseases in rats. *J Sport Health Sci* 2020;9:211–27.

various body systems, including the motor system,[10−12] metabolic system,[13−15] cardiocerebral vascular system,[16,17] nervous system,[17−19] and others.[20] This review focuses on the precise ways in which exercise by rats reduces disorders in several of these systems.

2. Methods

2.1. Data collection

PubMed was used as the data source. To collect research articles, we used the following terms to create the search: (exercise [Title] OR physical activity [Title] OR training [Title]) AND (rats [Title/Abstract] OR rat [Title/Abstract] OR rattus [Title/Abstract]). We also searched for articles related to cancer separately, using 3 keywords: cancer, exercise, and rat. To best cover targeted studies, we set 2 filters. First, the range of publication dates was set from January 1, 2008, to December 31, 2018, which yielded 4596 papers. We then limited these studies to those in which exercise worked as an intervention and were not simply assessments or capacity tests. Given these filters, 392 articles were included in our analysis.

2.2. Data analysis

The collected articles were categorized into 6 systems or disease types: motor system (17 articles), metabolic system (110 articles), cardiocerebral vascular system (171 articles), nervous system (71 articles), urinary system (2 articles), and cancer (21 articles). Each system was further subdivided into different types of diseases or related functions. Our review describes 4 common exercise methods—treadmill exercise, voluntary wheel running, swimming, and resistance training—and then compares and analyzes the effects on each system induced by the different exercise interventions. Details regarding the exercise methods are provided in the supplementary tables accompanying the article.

2.3. Classification of exercise types

2.3.1. Treadmill exercise

Treadmill exercise is a common exercise intervention applied in most research studies. The advantage of treadmill exercise is that the exercise intensity can be controlled artificially by regulating the speed or slope. If rats are unwilling to run, the researcher may poke their hindquarters softly or give them a low-level electric shock.

Prior to formal exercise intervention, rats are typically placed on the treadmill in advance to familiarize themselves with the treadmill environment. In most studies, rats ran from 10 min to 30 min each day at a low intensity with incremental speed. After the end of this adaptive training, the rats began the formal intervention, which used certain exercise intensities in fixed times. The studies determined the exercise capacity of rats by an exhaustion test, which was defined by 4 parameters obtained during the test: maximal oxygen consumption (VO_{2max}), maximal blood lactate, steady state, and maximal heart rate.

Our review defined intensity levels based mainly on a combination of all 4 parameters. Based on the articles reviewed here, the intensity of treadmill exercise was defined by running speed and treadmill slope and was categorized as follows: low intensity (<18 m/min; 0%−5% slope), moderate intensity (18−25 m/min; 0%−10% slope), and high intensity (>25 m/min; ≥0% slope).

As for exercise duration, most rats ran from 20 min/day 70 min/day in performing the training protocols, with a frequency of 5 days/week or 7 days/week. We defined 6 weeks as a tipping point for the duration of the whole training, with short-term training exercise lasting less than 6 weeks and long-term exercise lasting for 6 weeks or more. Acute exercise was defined as rats running at a fixed or incremental speed until exhaustion or running at fixed duration and speed for a single session.

2.3.2. Voluntary wheel running

Compared to treadmill exercise, voluntary wheel running enables rats to run at a relatively lower intensity for an unlimited time. Voluntary wheel running is usually chosen in order to minimize the potentially deleterious effects of treadmill running in Sprague-Dawley rats.[21] The distance that rats move in the cage can be monitored. For voluntary wheel running, rats also need adaptive training to familiarize themselves with the wheel environment. Generally, the rats are placed in a cage with a wheel for several days before the formal experiment.

In contrast to the treadmill exercise, the exercise intensity and duration of voluntary wheel running cannot be controlled. Thus, in our review we classified only the duration of exercise as short term (<6 weeks) or long term (≥6 weeks).

2.3.3. Swimming

Swimming is one of the most commonly used exercise interventions in rats. Rats can swim naturally, without producing strong resistance.[22] Sometimes rats swim freely, without any other interventions; on the other hand, to ensure the exercise intensity in a shortened swim time, rats usually swam with a workload (percentage of their body weight) attached to their tails. Before the rats swim, the water needs to be heated and maintained at a certain temperature (about 30°C). Rats should be dried immediately after they finish swimming. One week of adaptive training is usually necessary before the formal experiment, and exercise time is increased each day.

The intensity of swimming is determined by the following levels of daily exercise time and workload: low intensity (20−59 min/day, 0%−3% overload), moderate intensity (60−89 min/day, 0%−5% overload), and high intensity (≥90 min/day, ≥0% overload). As for duration, we used the same standard as for the treadmill exercise.

2.3.4. Resistance training

Resistance training has been proven to help athletes improve their performance.[23] However, in rats, resistance training is used less often than the other 3 interventions. Climbing a ladder with a load is a common method used for rats when conducting resistance training, but using electrodes on squatting rats to stimulate muscle contraction for jumping or having them wear Velcro vests with adjustable weights is also common in resistance training of rats.

The intensity of the electrode stimulation is defined by stimulation time. Most studies used 3 s of stimulation for 10 contractions, with a 7-s interval between contractions. Typically, 5 sets of stimulation occur, with 3 min of rest between sets. The intensity of ladder climbing or squat training is usually defined by completed repetitions and loaded weight on the rat. Ladder climbing or stair climbing usually occurs 8−12 times, with a gradually increasing load. Squat training typically involves 5 sets of 15 repetitions/session, with different groups having different weights in their Velcro vests. The duration of training is the same as for treadmill, with 6 weeks as the tipping point.

3. Results

3.1. Motor system

The motor system consists of 3 components: bones, joints, and skeletal muscles. The main functions of the motor system are movement, support, and protection.[24] Bones support the body and provide adhesion for muscle. Under the innervation of nerves, muscles contract and pull the attached bones, with the movable bone joint as a central pivot or fulcrum to generate lever movement.[25] If the motor system is damaged, bones, joints, muscles, and/or tendons will be affected, and corresponding clinical signs and systems will be apparent.

3.1.1. Skeletal muscle atrophy

Diverse physiopathological stimuli, including disuse, denervation, fasting, aging, and systemic diseases, can trigger skeletal muscle atrophy. Muscle atrophy is defined as muscle mass loss and muscle function impairment resulting from an increase in muscle protein degradation and decreases in protein synthesis.[26−28] A recent study has shown that overexpression of the transcription factor interferon regulatory factor 4 in brown adipocytes plays an important role in the prevention and treatment of skeletal muscle atrophy[29] and increases exercise capacity in muscle.

In our review of studies related to muscular atrophy, researchers often used resistance training and swimming. In Supplementary Table 1, treadmill exercise was performed on a motor treadmill at low or moderate intensity for acute or short-term duration, with a speed ranging 15−20 m/min and a slope of 0° or 20°. Two studies used short- or long-term resistance training as a training method.[30,31] One of the studies had the rats climb 1 m at an 80° incline, and weights used were calculated as a percentage of the body weight of each rat and were gradually increased by 10%, as tolerated, with a maximum weight of 50% body weight. The rats in the 2nd study climbed at 80% of maximal voluntary carrying capacity. All animals received adaptive training for 5−6 days to acclimate them to the climbing apparatus. In addition, a short-term exercise intervention combined low-intensity swimming with resistance training.

The exercise protocols described above showed positive effects on muscle mass, fiber-type redistribution, and skeletal muscle function. Only high-intensity treadmill exercise showed the negative effects of significant atrophy. For the positive effects, aerobic training enhanced muscle regeneration by inhibiting the ubiquitin-proteasome system through the leucine-rich protein 130/peroxisome proliferator-activated receptor γ coactivator-1α (LRP130/PGC-1α) complex; resistance training attenuated dexamethasone (DEX)-induced muscle atrophy via the mammalian target of rapamycin (mTOR) pathway and a small increase in the Muscle RING finger protein 1 (MuRF1) protein level.[31]

3.1.2. Muscle injury

Muscle injury is one of the most common diseases in orthopedics among athletes and nonathletes.[32,33] Excessive stretching or direct trauma to the muscle belly causes most of these injuries.[34]

In our review of studies using rat models of muscle injury (Supplementary Table 2), the main exercise protocols utilized were treadmill exercise and resistance training. High-intensity training for short-term duration was performed on the treadmill at an incrementally increased rate of speed. Speed ranged 10−30 m/min, with the slope ranging from 5° to 8°, and the study allowed all rats to run 10 min/day at 12 m/min for 5 days. In the training, rats began with an overload, gradually increasing from 60% to 80% of maximal voluntary concentric contractions, which was maintained until the end of training. In resistance training, the rats were familiarized with climbing the ladder (1.10 m × 0.18 m, 2 cm grid, 80° incline) for 3 days before the formal training.

These exercise protocols showed positive effects on muscle regeneration and recovery from the slow/oxidative phenotype. In resistance training, rats improved skeletal muscle regeneration through increased myogenic differentiation (MyoD) and myogenic factor 5 (Myf5) mRNA levels.[35]

3.1.3. Tendon injury

Tendon injuries are the major cause of musculoskeletal disorders.[36] Tendon conditions can be divided into many patterns: laceration at the musculotendinous junction, laceration of the central part of the tendon, avulsion fracture, contusion, or strain. When the tendon is severely damaged, the joint associated with the tendon is unable to stretch or bend due to loss of bone movement, resulting in disability.[37]

In studies using rat models of tendon injuries, treadmill exercise and resistance training were the main exercise methods used (Supplementary Table 3). Exercise training was performed on a motor treadmill at low intensity for short-term duration. In general, rats were subjected to 1−2 weeks of adaptive training on a treadmill device prior to the start of exercise training. Studies also used long-term resistance training as a training method. The load was gradually increased to 65%, 85%, 95%, and 100% of maximal voluntary concentric contractions. Rats were adapted to climbing a vertical ladder (1.10 m × 0.18 m, 2 cm grid, 80° incline) with no weight on the load apparatus for 2 nonconsecutive days.[38] In general, the rats used in these models of tendon injuries had surgically induced tendon injuries, or their injuries were the result of aging.

These exercise regimens usually had a positive effect on tendon remodeling or tendon injury in tendon-damaged rats.

Resistance training plays a potential role in preventing aging-related injuries such as tendon aging.[38]

3.1.4. Osteoporosis

Osteoporosis is a progressive metabolic bone condition characterized by profound loss of skeletal mass coupled with architectural deterioration, increases in bone fragility, and susceptibility to fractures.[39,40] Osteoporosis is found mainly in the elderly, resulting from an imbalance of osteoblast and osteoclast cells.[41] Degenerative changes in joints increase with the passage of time and age. In human joints, especially articular cartilage, varying degrees of decline and degeneration occur. Degenerative joint disease affects both soft and hard tissues, including cartilage, subchondral bone, and synovial membrane.[42] These conditions impair quality of life and increase mortality and morbidity rates.[43]

In osteoporosis studies in rats, the form of exercise intervention included mainly treadmill exercise, voluntary running wheel and resistance training (jumping exercise). In osteoporosis rat models, treadmill exercise training at moderate intensity was performed long-term with a fixed speed of 25 m/min with a 10° incline (Supplementary Table 4). Rats were adapted to the treadmill for 1 week using 5-min sessions at 15 m/min on a 15% grade.[44] For voluntary running wheel exercise, the long-term intervention was performed on rats with senile osteoporosis. Additionally, jumping training, a form of resistance training, was also used as an intervention method. The protocol consisted of 20 jumps/day. This was performed by placing the rat inside a wooden box. To elicit the first jump, the animal received an electric stimulation. With the stimulus, the animal jumped and grasped the upper edge of the box with the forelimbs and climbed onto a board; then the procedure was repeated.[45] After a week of adaptive training, the rats jumped as soon as they were placed in the box.

The protocols showed that all these exercise methods can prevent osteopenia through improving bone mineral density, reducing bone loss, and maintaining bone mass. However, their underlying mechanisms need further research.

3.1.5. Osteoarthritis (OA)

OA is the most common disease affecting the joints. It is characterized by a progressive degeneration of cartilage.[46] Clinical manifestations include joint pain, functional loss, tenderness, limited activity, crepitus, occasional effusion, and variable degrees of local inflammation. Pichler et al.[47] demonstrated that physical activity, specifically treadmill and vibration platform training, could be a therapeutic treatment for cartilage disease such as OA. Moreover, the combination of physical activity and a diet enriched by extra-virgin olive oil further improved the articular cartilage recovery process in early OA.[47] Another study also showed that exercise plays an important role in preventing OA disease and helping to preserve the articular cartilage and the entire joint.[48]

In rat models of OA, short-term or long-term training at low or moderate intensity was performed with a fixed or incremental speed that ranged 10−30 m/min and a slope of 3°−10° (Supplementary Table 5). The rats had adaptive training before the formal exercise program. Two studies showed that the rats became habituated to the treadmill after 10 min/day at 10 m/min for 1 week.[49,50] Short-term voluntary wheel running was also used, but treadmill exercise was the primary training method.

Treadmill exercise showed positive effects on inflammation and suppressed cartilage degeneration related to OA. Treadmill exercise can suppress monosodium iodoacetate-induced OA progression via inhibiting the nuclear factor kappa-B (NF-κB) signaling pathway.[49] Voluntary exercise may protect rats against OA pain, but the mechanism is not clear.[51]

3.2. Metabolic system

Catabolism and anabolism are the 2 processes essential for maintaining the normal condition of the human body and are the main components of metabolism. Metabolic disorders can lead to several diseases, including obesity, diabetes, and nonalcoholic fatty liver disease (NAFLD). It has been proven that exercise has positive effects on improving metabolic disorders.[10,52] This section of our review builds on the work of Goodpaster and Sparks,[53] who used exercise training as a tool to investigate the potential mechanism of energy metabolism in obesity and diabetes.

3.2.1. Obesity

Obesity is thought to influence the human lifespan and quality of human life by increasing the risk of developing diseases such as cancer, type 2 diabetes, depression, cardiovascular disease, and OA.[54,55] Many factors are involved in inducing obesity,[56] and lack of exercise is one of them. Thus, exercise is one of the important methods for fighting obesity.

In rat models in which obesity is diet induced, 3 exercise methods that have direct effects on obesity have been identified: treadmill exercise, voluntary wheel running, and swimming. At the beginning of the treadmill exercise protocol, the rats were adapted using a low-intensity running protocol for 10 min at 5−10 m/min.[57] Most formal exercise training was performed on a treadmill at moderate or high intensity for a short- or long-term duration, with a speed ranging 8−32 m/min and a slope ranging from 0° to 10° (Supplementary Table 6). Some studies also used voluntary wheel running as an exercise method. In these studies, wheel running was of long-term duration and was applied in a free exercise style (Supplementary Table 6). Additionally, some studies used short-term swimming (45 min/day, 5 days/week) and resistance training in experiments with obese rats (Supplementary Table 6).

These exercise protocols all showed positive effects on treating or preventing obesity by reducing weight, increasing insulin sensitivity, and improving energy metabolism in obesity-related signaling pathways. For example, in obese rats, swimming reduced obesity and hyperinsulinemia, inhibited insulin secretion induced by islet glucose, and restored the insulin-promoting effect with islet glucose-like peptide-1.[58] A single exercise bout reversed the insulin sensitivity of diet-induced obese rats and reduced the expression of inducible nitric oxide synthase and s-nitrosation of insulin receptor/insulin receptor substrate 1/protein kinase B, accompanied by an increase in the activity

of 5′ adenosine monophosphate-activated protein kinase (AMPK).[59] These results provide new insights into the mechanism of restoring insulin sensitivity during exercise.

3.2.2. Diabetes

Diabetes is a common disease that is due mainly to impaired insulin secretion and sensing.[60] Many medications have been used in treating diabetes, such as metformin, sulfonylureas, glucose-like peptide-1 analogs,[61] and other pharmacological treatments, along with caloric restriction and physical activity. Moreover, physical activity has already been proven to have a positive effect on life quality.[62]

Our review identified 3 exercise methods that have direct effects on diabetes, including treadmill exercise, voluntary wheel running, and swimming. In these studies, most rat models were Otsuka Long-Evans Tokushima Fatty (OLETF) rats. In most of the exercise protocols, usually using OLETF rats, exercise training was achieved through voluntary wheel running of long-term duration, with 24-h free access to the running wheel (Supplementary Table 7). Some studies also used treadmill and swimming as the exercise methods. In these studies, treadmill exercise was performed at moderate intensity at a speed of 20 m/min, and rats were forced to run 60 min/day for 12 weeks.[63] Also, long-term duration swimming was set at moderate intensity (Supplementary Table 7). One of these studies used a protocol of 150 min/week of swimming, and the other used a training time that increased incrementally every week.

These exercise protocols usually showed positive effects in preventing diabetes in male OLETF rats at different ages and in improving glucose metabolism and insulin resistance in rats with diabetes. After 3 weeks of moderate-intensity treadmill exercise, the serum levels of tumor necrosis factor α, cytokines 2α/β, interleukin-1, interleukin-6, C-reactive protein, and nonesterified fatty acid in rats with type 1 diabetes were significantly lower than those in sedentary rats.[64−66] It is suggested that moderate-intensity exercise may improve the metabolic disorder by reducing the inflammatory reaction in rats with diabetes.

3.2.3. Prediabetes

Prediabetes, including impaired fasting glucose level and impaired glucose tolerance, is the precursor of diabetes, which can be diagnosed only by high blood glucose levels. Diagnosing prediabetes is difficult, and 3 prevention methods have been suggested by the American College of Endocrinology and the American Association of Clinical Endocrinologists: healthful meals, reducing weight, and physical exercise.

In rats with prediabetes (impaired glucose regulation), treadmill exercise and voluntary wheel running were applied in most exercise protocols. Treadmill exercise was usually performed at low, moderate, or high intensity for short- or long-term duration at a speed ranging speed from 11 m/min to 27 m/min and a slope ranging from 0° to 15° (Supplementary Table 8). The rats were adapted to the exercise for 1 or 2 weeks before the formal exercise training in some studies,[67−70] whereas some experiments began with fewer than 5 days of familiarization or even none (Supplementary Table 8). The duration of voluntary running-wheel exercise ranged from a one-time experiment to long term, with 1 forced running-wheel training lasting 12 weeks. Acute swimming was also used in some studies.

The results shown in Supplementary Table 8 are consistent with those of Miranda et al.,[71] who showed that insulin-stimulated ribosomal protein S6 kinase 1 activation decreased after endurance training. One of the mechanisms by which exercise training enhances the insulin effect of skeletal muscle is the chronic activation of AMPK. AMPK is a known physiological inhibitor of the energy-consuming mTOR signaling pathway. In fact, interventions that reduce intracellular ATP levels or use the AMPK activator 5-aminoimidazole-4-carboxamide ribonucleoside can reduce mTOR activation, which can demonstrate the reduction of S6 kinase 1 phosphorylation levels. We observed that the exercise protocols reviewed in this study increased the phosphorylation of AMPK Thr172, which suggests that AMPK activation may be a possible mechanism that explains the inhibition of mTOR activation by exercise training. mTOR may be a potential target for the treatment of insulin resistance. Voluntary wheel-running exercise was shown to improve insulin resistance to some extent by inhibiting the expression of inducible nitric oxide synthase and subsequent s-nitrosation of protein kinase B (Akt).[72]

3.2.4. Metabolic syndrome

Metabolic syndrome refers to the pathological state of metabolic disorders of proteins, fats, carbohydrates, and other substances in the human body. It constitutes a complex group of metabolic disorders and a risk factor for diabetic cardiovascular and cerebrovascular diseases.[73] Studies have shown that exercise training has a positive effect on improving metabolic syndromes.

To investigate the variations of metabolic syndromes that are induced by altered lipid metabolism on diet-induced obesity in rats, Zucker Diabetic Fatty rats or OLETF rats were used in these studies. Exercise training was performed mostly on a treadmill at moderate or low intensity for short- or long-term duration at a speed ranging from 10 m/min to 30 m/min and at a slope ranging from 0° to 15° (Supplementary Table 9). Some studies also used voluntary wheel running as an exercise method. In these studies, wheel running training was applied in a free-exercise style of mostly long-term duration (Supplementary Table 9). Additionally, swimming 120 min/day for 4 weeks was also used in exercise training of rats (Supplementary Table 9).

These exercise protocols had different effects, always positive, on metabolic syndrome symptoms, such as triacylglycerol levels, lipid uptake, fatty acid oxidation, and other important factors. However, 1 study showed that acute exercise did not affect lipid uptake in muscle but, instead, led to a significant reduction in lipid uptake in the liver.[74]

3.2.5. NAFLD

NAFLD is one of many types of metabolic disease syndromes, including obesity, insulin resistance, hyperlipidemia, and type 2 diabetes.[75,76] Exercise has been proven to have significant therapeutic effects on NAFLD, although there are

many other treatment methods for humans such as lifestyle habits, including diet, food intake frequency, and sleep duration.[77,78]

In obese rats, or OLETF rat models, treadmill exercise and voluntary wheel running were most commonly used to treat NAFLD. Treadmill exercise was performed at moderate intensity for long-term duration at speeds ranging from 15 m/min to 20 m/min (Supplementary Table 10). In other studies, wheel-running training was applied freely for 4 weeks (Supplementary Table 10).

Notably, all these exercise interventions yielded positive results for preventing and treating NAFLD. Due to the disorder of glucose and lipid metabolism in NAFLD, blood glucose levels cannot be maintained within the normal range. With the continuous increase of insulin content, the secretory function and physiologic effects are weakened, eventually triggering insulin resistance and further aggravating the disease.[79] Studies have shown that active exercise improves insulin or glucose tolerance and insulin sensitivity in rats with NAFLD, whereas high-fat diets induce insulin resistance.[80] Liver steroyl-CoA desaturase-1 (scd-1) can improve the abnormal distribution of fatty acids by improving acetyl CoA carboxylase activity, increasing fatty acid oxidation and transferring the substrate to fatty-acid decomposition. The mechanism by which exercise regulates insulin may be through the activation of scd-1, which then regulates mTOR and sterol regulatory element-binding protein 1c-mediated lipogenesis.[81] Moreover, moderate long-term aerobic exercise can increase the activity of lipid metabolic enzymes and promote lipolysis and lipid use, thus preventing long-term ectopic deposition of lipids.[82]

3.3. Cardiovascular system

Sedentary lifestyle is a major risk factor for cardiovascular disease in humans.[15] Common cardiovascular diseases include myocardial infarction (MI), cardiac hypertrophy, myocardial injury, and atherosclerosis. Physical exercise is recommended as part of the rehabilitation for patients with heart diseases because it reduces the risk of heart disease, prevents myocardial damage, and improves heart function.[83,84]

3.3.1. MI

MI is a combination of coronary occlusion, interruption of blood flow, and partial myocardial necrosis due to severe persistent ischemia. After MI, the heart is characterized by decreased contractility and impaired cardiac structure (hypertrophy, dilation), cell death, adaptive remodeling of extracellular matrices, abnormal energy metabolism, and impaired filling due to cell dysfunction.[85]

Supplementary Table 11 shows that treadmill exercise and swimming in rat models after MI were the main exercise methods used in the studies reviewed here. Treadmill exercise was performed mostly for short- or long-term duration and included aerobic exercise and high-intensity training. For aerobic exercise, the exercise intensity was low or moderate, and exercise frequency was 2−7 times/week. For high-intensity training, the exercise frequency was 4−5 times/week at high intensity. Swimming was administered as either one-time exhausted exercise (where the rat was no longer able to keep its head above the water level consistently) or as long-term exercise 5−6 times/week. In addition, resistance training was sometimes used and always included 15−20 climbs/session with a 1−2-min rest between each session. Experiments with rats were of short-term duration and sometimes used an additional load of 0%−75% body weight. For swimming training, the duration was of long-term duration at moderate or high intensity. Only 1 study involved rats swimming with 3% of body weight overload as shown in Supplementary Table 11.

In general, the overall effects of exercise intervention were positive. Exercise induces cardiac muscle angiogenesis, reduces left ventricle (LV) contractile deterioration in postinfarction heart failure (HF), and alleviates mitochondrial dysfunction. The increased LV function may be related to a decrease in oxidative stress, which increases the antioxidant defense system and favorably affects angiogenesis in rats with MI. The decreased reactive oxygen species production may be an important mechanism by which exercise training mediates beneficial vascular effects in MI.

MI is usually accompanied by skeletal muscle abnormalities. Interval exercise training, resistance training, and moderate-intensity continuous aerobic exercise can all reverse MI-induced cardiac dysfunction and skeletal muscle atrophy by increasing antioxidant capacity and reducing oxidative stress and protein degradation in skeletal muscle. Mature brain-derived neurotrophic factor (BDNF) is induced by exercise training for skeletal muscle and the LV noninfarcted area, which may also contribute to improved muscle and cardiac function post-MI.[86] Studies using rats have also found that exercise training soon after MI attenuates myocardial fibrosis and maintains post-MI cardiac function. Swimming is also beneficial for post-MI cardiac remodeling because it relieves myocardial hypertrophy and contractile and relaxation dysfunction.[87]

3.3.2. Stroke

Stroke is the leading cause of disability and the 3rd highest cause of death in the world; it causes devastating complications that result in a significant burden for all of society.[88] The effectiveness of exercise has been reported in many animal experiments using cerebral ischemia models,[89] and treadmill exercise, which is used as a preventive intervention in rats, has been previously demonstrated to alleviate neuronal damage after cerebral ischemia.[89]

Supplementary Table 12 shows that the main exercise used in rats with middle cerebral artery occlusion is treadmill exercise. It was performed mostly at low to moderate or high intensity for short-term duration at a fixed or incremental speed ranging from 4 m/min to 30 m/min for 5−7 days/week; only 1 long-term duration study was identified. The rats were adapted to the treadmill apparatus at a speed of 5−9 m/min for 2−3 consecutive days before beginning the formal exercise training protocol. In addition, voluntary running wheel exercise of short-term duration and swimming were used for rats in a cerebral infarction model.

These exercise protocols showed positive effects on cerebellar stroke. Exercise can promote motor and cognition

functional recovery and improve neurologic function. One possible mechanism may involve enhanced proliferation and differentiation of hippocampal endogenous neural stem cells via the extracellular-signal-regulated kinase (ERK) signaling pathway, to inhibit neuronal apoptosis.[90]

Exercise preconditioning as a simple and clinically feasible preconditioning treatment has potential neuroprotective effects. The mechanism underlying exercise preconditioning might involve the regulation of the Toll-like receptor 4/NF-κB signaling pathway and the inhibition of central and peripheral inflammatory cascades in cerebral ischemia reperfusion injury.[91] It may improve cerebral blood flow, reduce infarct volume in the ischemic region correlated with angiogenesis in the ischemic cortex,[92,93] improve blood-brain barrier dysfunction by using the ERK1/2 pathway,[94] and reduce ischemic neuronal cell death through the 14-3-3γ/p-β-catenin Ser37/Bax/caspase 3 anti-apoptotic pathway.[95]

3.3.3. Cardiac hypertrophy

Cardiac hypertrophy is defined as the thickening of the cardiac muscle. The myocardial volume does not increase, and it sometimes becomes even smaller, but the whole heart looks larger than normal. The common cause of cardiac hypertrophy is the stenosis of the heart's exit, such as aortic stenosis and hypertension. Exercise can reverse pathologic cardiac hypertrophy into physiologic cardiac hypertrophy,[96] which produces a large number of new blood vessels in the epicardium as well as ventricular hypertrophy. The blood vessels are fully capable of coping with thickening of the ventricular myocardium.

As shown in Supplementary Table 13, hypertension-induced cardiac hypertrophy in spontaneously hypertensive rats may result in pathologic cardiac remodeling and ventricular dysfunction. For spontaneously hypertensive rats, swimming of long-term duration and moderate intensity 5 times/week was used as a method of exercise. The effects of swimming may reverse pathologic cardiac hypertrophy into physiological cardiac hypertrophy and increase clearance of reactive aldehydes and damaged proteins, thus reducing cardiac oxidative stress.[97,98]

3.3.4. Myocardial injury

Acute and chronic injury to the structure and function of the heart from various causes can lead to myocardial cell apoptosis,[99] increased myocardial inflammation,[100] and oxidative stress.[101]

As shown in Supplementary Table 14, the main exercise protocols for studying myocardial injury in rats were treadmill exercise and voluntary wheel running. The treadmill exercise was performed at high or moderate intensity for short-term and long-term durations at a frequency of 3−6 times/week. Before the formal exercise protocol, rats in 1 of the studies were familiarized to the treadmill for 12 consecutive days. The treadmill speed was progressively increased by 3 m/min every 2 days until the speed reached 18 m/min. The formal intervention time initially lasted for 5 min and was increased by 5 min/day to reach 60 min.[102] For the voluntary wheel running, short-term duration was used. The overall effects of the 2 exercise interventions—treadmill and voluntary wheel running—were positive.

Using the treadmill exercise at long-term duration and moderate intensity may help protect the organism against myocardial injury, which could be effective in reducing cardiac mitochondrial apoptotic, myocardial inflammation, edema, and fibrosis and increasing collagen content.[103−105] Voluntary wheel running also protected the heart against cardiac injury. This mechanism might be associated with decreased activity of matrix metalloproteinase 2.[106]

3.3.5. Atherosclerosis (AS)

AS is a pathologic condition that is the basis of several important adverse vascular events, such as angina, myocardial infarction, and spasm.[107] AS, the main cause of heart disease and stroke, is characterized by the accumulation of lipids and fibrous elements in the arterial wall.[108] In the early stages of AS, cholesterol accumulates in several arterial locations and brings about the formation of foam cells; foam cells lead to the growth of atherosclerotic lesions.

As shown in Supplementary Table 15, the main exercise protocol for studies of AS in rats was swimming. Swimming was long term in duration, at low intensity, with a frequency of 5 times/week. Adaptation for the swimming exercise was achieved by having the exercise time gradually increased for a week (for 5 min initially and then lengthened by 10 min daily for total 60 min).[109] In the formal exercise intervention, the exercise time was increased using a gradual step of 10 min on each subsequent day, starting from 10 min and extending up to 30 min or 60 min for 5 days/week.[110] In terms of its overall effects, swimming may improve blood circulation, blood lipids levels, and the vascular endothelium in rats. It also can be used as an anti-inflammatory therapy for AS.[111,112]

3.3.6. Hypertension

Hypertension is a systemic disease characterized by elevated arterial pressure and can be accompanied by functional or organic changes.[113] Increasing evidence suggests that exercise training is beneficial in the treatment of hypertension.[114]

As shown in Supplementary Table 16, the main exercise methods used for hypertension research in rats were treadmill exercise, voluntary wheel running, resistance training, and swimming. Treadmill exercise was the most commonly used type. It was usually performed for short- or long-term duration at either low, moderate, or high intensity 5−7 times/week. Voluntary wheel running was of short- or long-term duration, and rats had free access to running wheels. The resistance training was mainly of short- or long-term duration; a maximum repetitive test was performed, and the acute training intensity was maintained at 40%−50% of the maximum load. One long-term study was incremental in intensity, using 30%−60% maximum repetitive tests with rats performing 6−8 climbing sets.[115] Generally, all animals were familiarized with the exercise apparatus for 4−5 days. The duration for swimming studies was either short term or long term at moderate intensity, and exercise frequency was 5−7 times/week. Most experimental models used spontaneously hypertensive rat models.

The results from these studies indicated that moderate exercise training resulted in a beneficial adaptation of LV myocardial

mitochondria, improved cardiovascular autonomic balance, reduced blood pressure, and restored vascular and endothelial function in coronary. This might be related to the decrease of oxidative stress.[116,117] Furthermore, exercise has a protective effect on renal function in individuals with hypertension. It suppresses the hypertension-induced renal cortical inflammatory and fibrotic pathways, preserves mitochondrial function, and abates oxidative stress in the kidneys.[118] One study has also shown that exercise training before and during pregnancy in rats alleviates hypertension, angiogenic imbalance, and oxidative stress caused by placental ischemia in rats with uteroplacental perfusion.[119]

A study using resistance exercise improved endothelial function and lowered resting blood pressure in hypertensive rats. This may be associated with resting bradycardia and reduced cardiac sympathetic tone after training. Moderate swimming can also attenuate inflammation caused by hypertension and reactive oxygen species formation, lead to cardiac remodeling, modulate the calcium-handling protein expression in hypertensive rats, and prevent endothelial dysfunction through an increase in the expression of antioxidant enzymes.[115]

3.3.7. HF

HF is an important public health issue with high incidence and poor prognosis.[120] Several studies have indicated that exercise has beneficial effects on the myocardium in patients with HF and normalizes elevated sympathetic nerve activity in such patients,[121−123] but the underlying mechanism is unclear.

As shown in Supplementary Table 17, the main exercise methods used for HF research in rats were treadmill exercise, respiratory muscle training, and resistance training. Treadmill exercise was of short- and long-term duration at low and moderate intensity, and exercise frequency was 3−7 times/week. The respiratory muscle training was carried out for 30 min/day, 5 days/week, for 6 weeks. During the 1st week of the training, the rats were trained to breathe through the orifice at the inspiratory port attached to a rigid mask while confined to a whole-body cylinder. The inspiratory port was set at an internal diameter of 0.8 mm and was gradually decreased to a final internal diameter of 0.3 mm (maximal resistance) after 2 weeks.[124] For resistance training, the rats were subjected to a squat apparatus. An electric stimulus was applied to the rats' tails through a surface electrode. This repeatedly extended their legs and lifted the weight on the squat apparatus. To determine the training workload, all rats received a 1 repetition maximum test. The 1 repetition maximum was determined as the maximum weight lifted by the squat apparatus and was adjusted every 2 weeks. The resistance training program was based on 4 sets of 6−8 repetitions, 75%−85% of the 1 repetition maximum, a rest period of 90 s between sets, 3 times/week, for 8 weeks. All trained animals were subjected to the squat apparatus and performed 5−10 repetitions with 40%−60% of body weight for 1 week.[125] Aerobic exercise training may improve the inflammatory profile and cardiac function and attenuate cardiac remodeling in rats with HF. The mechanism by which exercise training alleviates elevated sympathetic outflow in HF may be through normalization of angiotensinergic mechanisms or glutamatergic mechanisms within the paraventricular nucleus. Upregulation of ATP-sensitive K^+ channels induced by chronic exercise may mediate some exercise-induced beneficial effects on cardiac function in postischemic HF. Moreover, exercise is associated with increased cytochrome oxidase activity in cardiac mitochondria and greater mitochondrial content of cardiolipin (a phospholipid is critical for mitochondrial energy metabolism), which provides new evidence that training may improve prognoses for hypertensive disease by preserving mitochondrial energy metabolism.[126,127]

Resistance training promotes improvement of cardiac function, strength gain, collagen deposition, and inflammatory response in rats with chronic HF. Short-term respiratory muscle training in rats with HF facilitates beneficial adaptations in hemodynamics, autonomic function, and pressure response.[128]

3.4. Nervous system

The nervous system, including the central nervous system and the peripheral nervous system, plays a leading role in regulating physiological and functional activities in the human body.[129] It is the system in which the various physiologic processes of various organs and systems are connected, interactive, and in close cooperation,[130] so that the human body becomes a complete and unified organism, enabling it to carry out all life activities.

3.4.1. Parkinson disease (PD)

PD is the most common extrapyramidal disease in middle-aged and elderly people. PD is a common neurodegenerative condition encompassing both motor and nonmotor symptoms. Even within pathologically defined patient cohorts, there remains a spectrum of clinical features, treatment responses, and prognoses.[131] So far, the main method for treating PD is medication, but in recent years, exercise as a treatment for PD has been more and more widely used.[132]

As shown in Supplementary Table 18, we found only 1 article exploring exercise intervention method in rats, and the method used was treadmill exercise in a rat model with PD.[133] The study was of short-term duration and used low-intensity exercise, with a fixed speed of 10 m/min, 30−40 min/day. The rats were familiarized with the treadmill exercise procedure for 1 day before the intervention. The study used adult male Wistar rats for research.

The treadmill exercise method showed a positive effect on modulating toxin-induced glial activation in rats with PD. Exercise can restore the decreased phosphorylation of ERK in striatum, which suggests that exercise can inactivate glycogen synthase kinase 3 through the neuroprotective effect of phosphorylation on the death of exercised attenuation of 6-hydroxydopamine-induced cells, and the cross-sectional area of type I and II fibers is significantly restored.[133] The expression of myosin heavy chain and Akt increased significantly, indicating that exercise can restore the loss of dopaminergic neurons and contralateral soleus atrophy caused by PD. The literature is consistent in showing that 30 min of fixed-speed treadmill training every day can also improve spatiotemporal gait injury, reduce inflammatory reaction in nerves, and improve walking

speed, dopamine transmission, and synaptic plasticity in cortical striatum.

3.4.2. Alzheimer's disease (AD)

AD is a neurodegenerative disease and is the most common cause of dementia. Clinically, it is characterized by memory impairment, aphasia, loss of recognition, visual-spatial impairment, executive dysfunction, and changes in personality and behavior. The etiology of AD is still unknown. It is estimated that 136 million people will be affected by dementia by 2050, which will present major global health and economic challenges. Currently, there is no treatment for AD; hence, AD provides the largest unmet medical need among neurologic disorders.[134,135] Currently, the treatment of AD is based mainly on drugs and diet. Exercise therapy is also being investigated as another option for treating AD.[136]

In the rat model of AD, the main exercise methods included treadmill exercise and swimming (Supplementary Table 19). The most commonly used exercise method was treadmill exercise; the frequency of all treadmill exercise was 5 days/week, with exercise performed at low intensity.[137] Researchers trained the rats to use the treadmill with a fixed or incremental speed of about 10−15 m/min, and the rats were treated for 4 weeks. Rats were familiarized with the treadmill exercise procedure at a speed of about 5 m/min before the intervention. Swimming was also used as a method of exercise for AD. In the swimming studies, swimming was usually at a low intensity. The exercise intensity differed; in one of the studies, rats swam only once for 15 min each time, whereas in a 2nd study, they swam 10 min to 1 h each time. These studies used mainly adult male Wistar or Sprague-Dawley rats for research.

The treadmill and swimming exercise methods showed positive effects in the expression of BDNF, change of hypothalamic-pituitary-adrenal axis, or increased levels of amyloid precursor protein in rat models of AD. Four weeks of treadmill exercise prevented the down-regulation of calmodulin-dependent protein kinase IV level induced by AD, suggesting that exercise can maintain normal cyclic adenosine monophosphate response element-binding protein phosphorylation and a complete late-phase long-term potentiation even under the toxic impact of amyloid β 1−42. Exercise may be an effective neuroprotective agent to protect cerebral nerves from excessive injury by upregulating BDNF.

3.4.3. Depression

Depression is characterized by persistent low mood and is the main type of emotional disorder. Depression is one of the most prevalent mental illnesses among adolescents and often occurs during adulthood as well.[138] Despite the significance of depressive disorders, less than 50% of depressed adolescents receive treatment,[139] suggesting that effective measures to prevent depression are needed and should be widely implemented. The treatment of depression is mainly based on drug therapy and cognitive therapy, but exercise intervention has also been shown to have a positive effect on depression.[140]

For research in depressed rats, the main exercise methods included treadmill exercise and swimming. In Supplementary Table 20, treadmill exercise was of short-term duration and was performed at low intensity for 5 days/week in most studies. As for speed, rats ran on a treadmill with fixed or incremental speed ranging 15−20 m/min.[141] In addition, the rats were familiarized with the procedure for 5 consecutive days before the formal exercise training. Some studies used swimming as an exercise method. In these studies, swimming was of short-term duration at low intensity, and rats were exercised freely. Studies usually used adult male Wistar or Sprague-Dawley rats for research.

These exercise methods had positive effects on the expression of BDNF in the hippocampus.[142] They also helped to protect the capillaries in white matter, changed the hypothalamic-pituitary-adrenal axis, and promoted the long-term potential of the hippocampus in depressed rats. Treadmill exercise upregulated the 5-hydroxytryptamine receptor, promoted 5-HT synthesis, and improved depressive symptoms, hippocampal neurogenesis and he BDNF/proBDNF ratio in ischemic hippocampus of rats with poststroke depression. The biomarkers of depression may also be affected by treadmill exercise.[143]

3.4.4. Anxiety

Anxiety, also known as anxious neurosis, is the most common type of neurosis and is characterized by being nervous, worried, and restless. Anxiety disorders are the most common mental health disorder in childhood, affecting approximately 12%−20% of youth.[144] Anxiety disorders are associated with pronounced functional impairments and reduced quality of life across the lifespan.[145] The treatment of anxiety is based mainly on drug therapy, but exercise therapy can also relieve anxiety effectively.

As shown in Supplementary Table 21, two common exercise training types were used for rats with anxiety. The most common exercise method was treadmill exercise of short-term duration at moderate intensity for 5−7 days/week, with a fixed or incremental speed of about 15 m/min.[146] The rats were familiarized with the procedure for 7 consecutive days before beginning the exercise-raining protocol. Newborn Wistar rats and male Sprague-Dawley rats were used. Researchers also used swimming as an exercise method. In these studies, rats swam freely for short-term duration. These studies usually used adult male Sprague-Dawley rats.

These exercise methods showed positive effects on expression of neurotrophins in anxious rats. Exercise training such as treadmill running can reduce the oxidative stress in the brain regions of rats, which is related to the anxiety response and can prevent anxiety-like behaviors in rats.[147,148]

3.4.5. Neuropathic pain

As shown in Supplementary table 22, neuropathic pain usually resists traditional treatment, severely reduces quality of life, and presents a heavy financial burden to society. Physical activity is becoming an important part of rehabilitative treatments for patients suffering from acute or chronic pain. Exercise alleviates various types of chronic pain, including pain after spinal cord contusion, lower back pain, chronic musculoskeletal pain, complex regional pain syndrome type I, and noninflammatory chronic muscle pain.[149,150] Neuropathic pain is generally treated

through surgery, but 1 preliminary study found that exercise therapy can be used to treat neuropathic pain.

In Supplementary Table 22, only 1 study using rat models examined the relationship between exercise training and neuropathic pain. This study used swimming as a method of exercise. The intervention was of short-term duration (4 consecutive weeks) and was done for 5 days/week with 10−60 min/day of free swimming. The study used adult male Sprague-Dawley rats.

Swimming exercise usually showed positive effects in the expression of neurotrophins in rats with neuropathic pain. Low- and moderate-intensity exercises can reduce oxidative stress and relieve neuralgia by regulating the activation of glial cells and the expression of BDNF in the dorsal horn of ipsilateral spinal cord.

3.4.6. Nerve injury

The nervous system is a functional regulatory system that plays a leading role in the human body. Once nerve damage occurs, it has an impact on all parts of the body. Nerve injuries include prominent neuronal damage, intersynchronous signaling disorders, and spinal cord injuries.

Many studies using rats concentrated on the relationship between exercise and nerve injury. The 3 most common types of exercise included treadmill exercise, swimming, and voluntary wheel running (Supplementary Table 23). The most commonly used exercise method was treadmill exercise. These studies were of short-term duration (4−6 consecutive weeks). Exercise was performed at low or moderate intensity 5−7 days/week, with a fixed or incremental speed of about 15−25 m/min. The rats were familiarized with the procedure for 3−7 consecutive days before beginning the exercise-training protocol. Other studies used swimming as an exercise method. In these studies, swimming was of short-term duration (4 consecutive weeks) and was performed 5 days/week with free exercise. The remaining studies used voluntary wheel running as a method of exercise. In these studies, voluntary wheel running was performed at low intensity for a short-term duration. All these studies used adult male Sprague-Dawley and Wistar rats.

These exercise methods showed positive effects on modulating changes in DNA methylation, increasing glial cell line-derived neurotrophic factor protein content and inducing BDNF expression or reducing the expression of central cannabinoid receptors of nerve-injured rats. Physical activity promotes the recovery of neurons in the corticospinal tract, suggesting the potential causes of atopic pain. The BDNF promyosin-associated kinase B (TrkB) receptor is expressed in abnormal fibers. Blocking the BDNF-TrkB signal can significantly inhibit the abnormality. Therefore, early rehabilitation of spinal cord injury may cause atopic pain through the BDNF-TrkB signaling pathway.

3.4.7. Traumatic brain injury (TBI)

TBI is a main cause of disability or even death in developing and developed countries.[151] TBI occurs as a result of a direct mechanical injury to the brain and induces central nervous system degeneration and neuronal cell death.[152]

Supplementary Table 24 shows that the main exercise forms used in studies involving rats with TBI were treadmill exercise and swimming. One exercise training was performed on a treadmill at low to moderate intensity for a short-term duration, performed 5 or 7 days/week at a fixed or incremental speed (Supplementary Table 24). The rats were adapted to the treadmill apparatus for 7 consecutive days before beginning the exercise-training protocol by having them exercise 15 min/day at 15 m/min. Two studies used swimming as an intervention. These 2 studies were of short-term and long-term durations, with exercise performed 5−7 days/week for 20 min/day or 90 min/day.

The results of these studies showed a positive effect on brain-injury treatment. Exercise following TBI can inhibit neuronal degeneration and apoptotic cell death around the damaged area, which can lead to improvement in cerebral dysfunction.[153]

3.4.8. Cerebellar ataxia

Cerebellar ataxia is an inherited and progressively degenerative disorder[154] that affects approximately 2.63 million people worldwide. Clinical studies have reported that treatment with drugs has produced limited results, but treadmill exercise has recently yielded significant benefits and improvements.[155]

Supplementary Table 25 shows that only 2 studies involving rats with cerebellar ataxia were performed. Treadmill exercise was performed at low to moderate intensity for a short-term duration at a fixed speed of 15 m/min and a slope of 10° (Supplementary Table 25). The studies used Spastic Han Wistar rats.

Although the data from these 2 studies are not sufficient to allow certainty, it appears that moderate exercise at least partially ameliorates cerebellar dysfunction in Spastic Han Wistar rats by increasing the lifespan and improving motor function.

3.4.9. Epilepsy

Epilepsy is one of the most common neurological diseases. The main functions of existing drug therapies are to reduce overexcitation and prevent seizures, but these treatments fail to affect potential pathophysiological disorders.[156] Many patients with epilepsy have a wide range of cognitive problems in learning, memory, attention, and executive control.[157] These cognitive deficits lead to a decline in the quality of life and are associated with many factors, including the etiology of epilepsy, recurrent seizures, and the side effects of antiepileptic drugs, or a combination of these factors. Research in the field of sport in the treatment of epilepsy has shown positive results. Further investigation is necessary to establish the relationship between sports activities and epileptic cognition.[158]

As shown in Supplementary Table 26, the most frequently used exercise method in research on rats with epilepsy involved treadmill exercise. Exercise time was 20−30 min/day at 12−14 m/min, and most of the adaptive training was conducted for 10 min/day at a speed of 10 m/min with 0° inclination. Compared to the group with epilepsy, the activation of the cAMP response element binding protein was increased in the group with epilepsy and exercise.

These results suggest that the beneficial effects of exercise on the brain of patients with epilepsy may be partially related

to the activation of proteins related to the BDNF-TrkB signaling pathway.[159] Moderate long-term physical exercise can reduce the incidence of epilepsy caused by TBI.[160]

3.4.10. Autism

Autism is a neurological disease that occurs in childhood and is characterized by social and communication disorders. Cerebellar abnormalities in autistic patients include Purkinje cell losses and dyskinesia.[161] Abnormal cerebellar structure in autistic patients includes loss and atrophy of granular and Purkinje cells.

As shown in Supplementary Table 27, studies conducted in autistic rats had young rats run on a treadmill for 30 min/day, 5 times/week, for 4 weeks. The exercise protocol for the exercise group included a speed of 2 m/min for the 1st 5 min, 5 m/min for the next 5 min, and 8 m/min for the next 20 min, all without a slope.

Kim et al.[162] suggested that the expression of B-cell lymphoma-2 in the cerebellum of autistic rats decreased, and the expression of Bax increased. In contrast, treadmill exercise enhanced the expression of B-cell lymphoma-2, inhibited the expression of Bax, and increased the expression of glutamate decarboxylase 67 and cyclin D1 in the cerebellum of autistic young rats. Treadmill exercise also improved the motor dysfunction of young autistic rats. Other mechanisms remain unclear.

3.5. Urinary system

Diseases can occur in the organs of the urinary system (kidney, ureter, bladder, and urethra) and spread to the whole system. Symptoms are manifested mainly in the urinary system itself, such as urination changes, urinary system changes, masses, and pain, but other symptoms can also occur, such as hypertension, edema, and anemia. Urinary diseases may also lead to glomerulonephritis, urolithiasis, and renal failure.[163]

3.5.1. Chronic kidney disease (CKD)

The physical performance of patients with CKD is impaired at the the early stage of the disease. Injuries are a key medical problem in patients with CDK because their reduction in physical activity seriously affects their prognoses.[164]

Supplementary Table 28 shows that the main exercise method used in studies of rats with CKD was treadmill exercise, which was most often performed at moderate intensity of short-term duration at a stable or incremental speed. The adaptation protocol used was Day 1: 10.0 m/min × 10 min; Day 2: 12.5 m/min × 15 min; Day 3: 15.0 m/min × 20 min with 5° incline; Day 4: 17.0 m/min × 25 min with 10° incline; Day 5: 17.0 m/min × 30 min with 15° incline. Most treadmill training regimens were for 30−60 min/day for 5 days/week.

Exercise has been shown to be an increasingly effective method in the treatment of patients with CKD, resulting in improved physical health, cardiovascular health, and quality of life.[165] Current international guidelines recommend that patients with CKD participate in a health-appropriate cardiovascular exercise program for 30 min/day, 5 days/week.[166]

As Supplementary Table 28 shows, moderate exercise is beneficial to the recovery of gentamicin-induced acute renal injury and can optimize the removal and recovery of renal tubules and protect the kidney from future toxic drugs and even from aging. Exercise has been recommended for the treatment of muscle atrophy in adult patients with CKD.[167]

3.6. Cancer

Cancer refers to a malignant tumor originating from epithelial tissue and is the most common type of malignant tumor.[168] The occurrence of cancer is associated with smoking, infection, occupational exposure, environmental pollution, unhealthful diet, and genetic factors.[169] As the average life expectancy of human beings increases, the threat of cancer has become increasingly prominent, and it has become the number one cause of death for urban and rural residents in China.

3.6.1. Breast cancer

Breast cancer is the most common cancer and is the 2nd leading cause of cancer deaths in women in developed countries.[170] The pathogenesis of breast cancer is generally related to heredity. It is one of the most common malignant tumors and seriously affects and even threatens women's lives. Breast cancer is generally treated with surgery and chemotherapy. Exercise can also be used as a therapeutic method for treating and preventing breast cancer.[171]

As shown in Supplementary Table 29, the main exercise methods used in rat models of breast cancer included treadmill exercise, voluntary wheel running, and forced wheel exercise. The treadmill exercise was typically of short-term duration performed at low or moderate intensity and was conducted 5 days/week[172,173] with a fixed or incremental speed of about 20 m/min. The studies using voluntary wheel running were of short-term duration, usually performed at low intensity for 7 days/week with free access to the wheel. Additionally, some studies used forced wheel exercise as an exercise method; forced wheel exercise was of short-term duration at low intensity for 5 days/week. These forced wheel exercise studies usually used adult female Sprague-Dawley rats and Wistar rats.

Exercise methods usually showed positive effects for preventing breast cancer.[174,175] The mechanisms may include the prevention of tumor-induced tumor necrosis factor-like weak inducer of apoptosis/NF-κB signaling, the activation of AMP-activated protein kinase, downregulation of mTOR-related signaling, and the inhibition of the carcinogenic response.

3.6.2. Colon cancer

Colon cancer is the most common malignant tumor in developed countries such as Western Europe and North America. The incidence and mortality due to colorectal cancer is the highest in China.[176] The incidence of colon cancer is related to the social environment, lifestyle, and genetic factors. However, the exact causes of colon cancer are not clear. Colon cancer generally requires surgery and medication. Exercise therapy is also used as a treatment for patients with colon cancer.[177]

Supplementary Table 30 shows that in rat models with colonic cancer, the main exercise methods included swimming and

voluntary wheel running. Swimming was the most commonly used method of exercise. It was of short- or long-term duration performed at low or moderate intensity 5−7 days/week, with free exercise. One study used voluntary wheel running performed at low intensity for short-term duration. These studies often used the adult male Wistar rats for research.

These methods of exercise can upregulate the expressions of antiproliferation, anti-inflammatory, and AMPK factors in rats with colon cancer.[178]

3.6.3. *Other cancers*

Patients with chronic diseases, such as infectious diseases and malignant tumors, often experience cachexia with the deterioration of the disease. Cachexia is characterized by behavioral and metabolic symptoms.[179] The severity of cachexia varies with the disease and by individual, so it is difficult to define and diagnose. It is often accompanied by the rapid deterioration of body fat and muscle, which not only affects the quality of life of patients but also is often the main cause of morbidity and mortality.[180]

Supplementary Table 31 shows that the main methods of exercise used in tumor-bearing rat models include treadmill, swimming, and resistance training (climbing). The protocols included 8 weeks of exercise, 5−7 days/week. As Supplementary Table 31 shows, exercise reduced the tumor-survival area, and sport-oriented animals showed fewer active tumor cells, smaller tumor volume, smaller tumor size, and increased weight. Wistar male rats were commonly used in these studies.

These results suggest that exercise may regulate the physiological and microenvironment of the tumor, weakening the invasiveness. However, the molecular mechanism of the effect of exercise on tumors remains to be clarified. The increase in energy expenditure caused by exercise training can reduce the energy supply the tumor needs for survival. In short, if the energy is insufficient, especially in the glycolysis pathway, it can affect the growth of tumor cells.[181]

4. Conclusion

In this review, we summarized the effects of exercise on various diseases in 6 systems as it related to studies involving rats. We analyzed the kinds of exercise and the types of exercise interventions that were shown to be effective in treating diseases or changing signaling pathways. The use of rat models also provides convenience for researchers in producing other models. For example, for attention deficit disorder, a disease of the nervous system, the use of rat models may be more parallel with the model of attention deficit disorder in humans because of the larger size of rats, better observational conditions for their tissues and organs, and easier collection and analysis of their cerebrospinal fluid.

Taken together, these studies have shown that exercise can have positive effects on most diseases, or at least can alleviate the diseases and their symptoms. However, the parameters of exercise, such as exercise duration and intensity, can make a difference. Specifically, long-term exercise (lasting 6 or more weeks) may be the most effective way to treat diseases involving the motor, metabolic, and cardiovascular systems, whereas exercise of short-term duration (lasting fewer than 6 weeks) is possibly a better choice for treating psychological disorders. Differing exercise intensities can also lead to a reversed phenotype. Therefore, researchers should carefully choose exercise training protocols for their own studies to avoid unexpected results. Given the huge demand for information, our review aims to fill this gap and provide guidelines for using rat models in exercise-intervention research. To better show our results, we summarize the exercise intervention methods for different systems in Table 1.

However, this review has many areas for improvement. Compared with studies using mouse models, studies using transgenic rat models are generally more difficult to develop due to physical factors, which partially impede their range of use and the study of the mechanisms affecting outcomes. The

Table 1
The suggested exercise interventions for different systems in rats.

System	Exercise method	Exercise protocols			
		Adaptive training	Duration	Frequency	Intensity
Motor	Treadmill exercise	Consecutive 1−2 weeks, 15 min/day	4−8 weeks	5 days/week	60 min/day, 10−20 m/min
Metabolic	Treadmill exercise	Consecutive 1−2 weeks	8−10 weeks	5−7 days/week	60 min/day, 20−25 m/min
Cardiocerebral vascular	Treadmill exercise	5−9 m/min, increased 1 m/min every day, 2−3 days	4−8 weeks	5 days/week	60 min/day, 50%−60% of maximal exercise capacity
Nervous	Treadmill exercise	Consecutive 3−7 days	4−8 weeks, 6−8 months	5 days/week	30 min/day, 10−22 m/min
Urinary	Treadmill exercise	Day 1: 1.0−10.0 m/min × 10 min; Day 2: 12.5 m/min × 15 min; Day 3: 15.0 m/min × 20 min with 5° incline; Day 4: 17.0 m/min × 25 min with 10° incline; Day 5: 17.0 m/min × 30 min with 15° incline	4−6 weeks	5 days/week	30−60 min/day, 16−17 m/min
Cancer	Treadmill exercise	Consecutive 3−5 days	8−12 weeks, 35 weeks	5 days/week	60 min/day, 20 m/min
	Voluntary wheel exercise	Consecutive 2−3 days	4−6 weeks	7 days/week	free to exercise

studies included in our review focused mostly on improving intervention protocols rather than on investigating underlying mechanisms. Therefore, we urge that more attention be paid to accelerate the development of the entire system related to rat models, thus providing more meaningful results and the conclusions derived from these studies.

Given the rapid development of research in this area, annual updates of this review are needed to keep pace with the latest findings regarding the relationships between exercise and disease treatment and prevention.

Acknowledgment

The study was funded by grant from the Chinese Postdoctoral Science Foundation: 2019M651553.

Authors' contributions

All authors were involved in the development of this review article. DG helped collect articles; QT prepared all tables; RW wrote the main text; HT designed and coordinated the article; TY was responsible for the discussion; XK summarized sections of the paper. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

Supplementary materials

Supplementary materials associated with this article can be found in the online version at 10.1016/j.jshs.2019.09.008.

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