

Effects of exercise on brain functions in diabetic animal models

Sun Shin Yi

Sun Shin Yi, Department of Biomedical Laboratory Science, College of Medical Sciences, Soonchunhyang University, Asan 336-745, South Korea

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Correspondence to: Sun Shin Yi, DVM, PhD, Assistant Professor, Department of Biomedical Laboratory Science, College of Medical Sciences, Soonchunhyang University, 646, Eupnae-ri, Sinchang-myeon, Asan 336-745, South Korea. admiral96@sch.ac.kr

Telephone: +82-41-5304873

Fax: +82-41-5308085

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Abstract

Human life span has dramatically increased over several decades, and the quality of life has been considered to be equally important. However, diabetes mellitus (DM) characterized by problems related to insulin secretion and recognition has become a serious health problem in recent years that threatens human health by causing decline in brain functions and finally leading to neurodegenerative diseases. Exercise is recognized as an effective therapy for DM without medication administration. Exercise studies

using experimental animals are a suitable option to overcome this drawback, and animal studies have improved continuously according to the needs of the experimenters. Since brain health is the most significant factor in human life, it is very important to assess brain functions according to the different exercise conditions using experimental animal models. Generally, there are two types of DM; insulin-dependent type 1 DM and an insulin-independent type 2 DM (T2DM); however, the author will mostly discuss brain functions in T2DM animal models in this review. Additionally, many physiopathologic alterations are caused in the brain by DM such as increased adiposity, inflammation, hormonal dysregulation, uncontrolled hyperphagia, insulin and leptin resistance, and dysregulation of neurotransmitters and declined neurogenesis in the hippocampus and we describe how exercise corrects these alterations in animal models. The results of changes in the brain environment differ according to voluntary, involuntary running exercises and resistance exercise, and gender in the animal studies. These factors have been mentioned in this review, and this review will be a good reference for studying how exercise can be used with therapy for treating DM.

Key words: Diabetes mellitus; Involuntary and voluntary exercise; Resistance exercise; Brain function; Animal models

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Core tip: Brain is a highly sensitive and vulnerable tissue easily influenced by diabetes mellitus (DM). Physical exercise has been known to be one of the best non-pharmacologic ways to prevent and treat DM. Animal exercise experiments are very useful for research on DM because experiments cannot be performed in humans. Exercise has various benefits that help to improve brain function by reducing chronic inflammatory responses, accumulation of adipose tissue, appetite, insulin resistance, and dysfunction of the negative

feedback mechanism. In this review, the author reports a battery of animal models of exercise, and presents the beneficial effects of exercise on the brain.

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INTRODUCTION

Diabetes mellitus (DM) is one of the most common endocrine disorders and is mainly divided into two types according to the activity of β -cells in the pancreas: type 1 DM (T1DM) is characterized by degeneration of β -cells, while the main cause of type 2 DM (T2DM) is a progressive decline in insulin sensitivity resulting in sustained hyperglycemia^[1-3]. Particularly, DM is known as the main factor that can cause various pathologic brain complications and can promote cognitive impairment and vascular dementia in humans^[4-8]. A number of studies have reported that DM can cause hormonal dysregulation, systemic vascular changes, dysregulation of the plasma glucose level, changes in blood chemistry, and other organ dysfunctions such as kidney and heart failure^[9-19]. Various medical treatments are available to regulate glucose dysregulation, correct hormonal changes and vascular conditions in DM patients; however, these medical treatments cannot always cure the metabolic disorder completely, and physicians also cannot predict the progression of the complications with uncontrolled patient's life styles^[20-24].

Particularly T2DM is significantly related to the incidence of obesity and its associated disorders^[25-27]. Obesity is defined as a surplus of body fat accumulation, with the excess of adipose tissue really being a well-established metabolic risk factor for the development of obesity-related comorbidities such as insulin resistance, T2DM, cardiovascular diseases, and some common cancers^[2,28-32]. The mechanisms linking excess adiposity and cancer are unclear, but the obesity-related low-grade chronic inflammation is widely accepted as a critical factor in the pathogenesis of various diseases such as T2DM, cardiovascular disorders, dementia, cancers, dietary control failure^[26,28,33-42]. Currently, particular attention has been placed on the pro-inflammatory microenvironment in the body associated with obesity, specifically underlining the involvement of obesity-associated hormones/growth factors in the cross-talk between macrophages, lymphocytes, adipocytes, and epithelial cells involved in the development of T2DM^[28,43]. In addition, accumulated peripheral white adipose tissue (WAT) is an endocrine tissue that secretes hundreds of cell-signaling molecules known as cytokines, chemokines, and adipokines^[29,32,33,44,45]. The endocrine

function of adipose tissue might be a key factor in the mechanisms linking adipose tissue to insulin resistance, leptin resistance, dietary control failure, T2DM-associated dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, neurodegenerative diseases, vascular diseases related to aging, cognitive impairment, and dementia^[27,35,45-50]. Hence, uncontrolled chronic obese condition can be a critical factor in the development of T2DM, and it also acts as an agent that affects normal brain functions.

Recently many studies have shown the positive effects of regular physical activity on improving complications caused by DM, and hence regular physical activity intervention is regarded as a promising adjuvant therapy^[7,37,51-62]. Exercise can affect various physical environments and has decisive effects on improving brain functions for a better quality of life^[7,59-61,63-72]. However, the precise mechanisms responsible for the positive effects of exercise on brain functions under obesity and T2DM conditions have not yet been well understood, and many studies have been performed using animal models of different diabetic stages regardless of the DM type and under various kinematic conditions to assess the related mechanisms for changing the microenvironment of the brain. Thus, experiments with animal exercise models mimicking the etiology and progression of human DM have been actively performed and developed to assess the preventive and therapeutic effects of exercise on brain functions^[1,73-81].

Therefore, we review recent evidences on the role of exercise in promoting brain functions mainly under T2DM conditions in animal models and provide practical applications for the management of T2DM.

PHYSIOPATHOLOGICAL CHANGES CAUSED BY DM

Most of the DM conditions gradually impair normal brain functions by causing excessive production of pro-inflammatory cytokines, insulin resistance, and reactive oxygen species due to certain causes such as prolonged obese condition or hormonal dysfunction^[15,27,28,31,32,35,82-88]. Excessive and/or compulsive overeating disturbs the normal blood composition, deteriorates cardiovascular circulation, induces insulin resistance, and increases the visceral fat^[29,45,82,89-91]. Particularly, the infiltrated inflammatory immune cells such as macrophages and lymphocytes in adipose tissues secrete a variety of cytokines into the blood stream, and negatively influence the systemic cardiovascular system and the brain^[32,44,82,92-94]. A number of studies have shown that elevations in levels of systemic inflammatory mediators such as adipokines, tumor necrosis factor- α , resistin, interleukin-6, plasminogen activator inhibitor-1, C-reactive protein, monocyte chemoattractant protein (MCP)-1 play a pivotal role in changing the physiology of the brain^[3,45,56,82,95-98]. Particularly, results of animal

and human studies have showed that insulin passes *via* the systemic circulation to the brain and it may have some physiologic actions which are different than its peripheral metabolic effects. Insulin resistance in peripheral tissues leads to the elevation of pro-inflammatory cytokines, neurotoxic ceramides, obesity-induced NADPH oxidase-associated oxidative stress in the brain, and insulin action on the brain is thought to be a regulator of peripheral glucose homeostasis in rodent studies *via* melatonin related mechanisms, increased unfolded protein response activation, mitochondrial and ER stress related overeating, leptin and insulin resistance, corticotropin-releasing factor-related islet cell control^[47,67,99-102]. Recent studies of the mouse brain have demonstrated that degenerative plaque formation observed in AD (AD is the most prevalent form of dementia) is associated with insulin resistance^[47,103]. Insulin regulates food intake and cognitive functions in the brain; however, deranged insulin signaling in the brain has also been implicated in neurodegenerative disorders^[104-107].

Insulin action in the brain is regarded as the main factor for maintaining DM patients in a healthy condition due to the interrelationship between peripheral and central insulin resistance.

ANIMAL MODELS IN DM RESEARCH

DM is a chronic disease that is characterized by a relative or absolute lack of insulin release, resulting in hyperglycemia. Since T1DM and T2DM, as endocrine disorders, represent quite complex diseases in which different organ systems are involved, animal models should be chosen carefully depending on what aspect of the disease is being investigated. On the other hand, for developing specific models of T1DM and T2DM, investigators should be aware of the different pathogenic mechanisms of DM that involve different inducible factors.

T1DM animal models

The main characteristic of T1DM is autoimmune destruction of the pancreatic β cells, leading to lack of insulin release. In animal models, investigators can induce this deficiency by chemical ablation of the beta cells in breeding animals that spontaneously develop the autoimmune diabetic condition. The representative chemicals that induce T1DM are streptozotocin synthesized by *Streptomyces achromogenes*^[108-110], and alloxan^[1,73,111,112] which causes poor β cell defense mechanisms against free radicals. Thus, these chemicals can be used for developing new insulin, transplantation models for testing treatments that may prevent beta cell death. However, the researchers should be aware that a number of studies using STZ did not consider the time period between chemical injection in animals and sacrifice. Thus, it is true that many researches on T1DM using STZ injection have ignored this factor. Shin *et al*^[110] and Yi *et al*^[113]

demonstrated chronological hippocampal changes in the brain at different time points of animal sacrifice after STZ injection. Therefore, researchers should remember that the results of T1DM *via* the chemical might be different based on how many days or weeks have passed following chemical administration in animals.

The non-obese diabetic mice, Biobreeding rats, and LEW. 1AR1/-iddm rats are the most commonly used animal models of spontaneous autoimmune diabetes showing beta cell destruction due to an autoimmune process^[1,73,75]. Akita mice, a genetically induced insulin dependent T1DM diabetic animal model, are characterized by beta cell destruction *via* ER stress. Lastly, T1DM can be induced by viruses such as Coxsackie B virus^[114], Encephalomyocarditis virus^[115,116], and Kilham rat virus^[116,117]. The virus-induced model can be complicated as the outcome is dependent on replication of the virus as well as timing of the infection^[118].

Several other large animal models except for rodent animals have been developed to study T1DM extensively. Since it is relatively difficult to expect the development of spontaneous diabetes in large animal models, induced models of T1DM are required. The most commonly used method of inducing T1DM in large animal models is by performing pancreatectomy and chemical ablation of beta cells (STZ)^[119-122]. The T1DM rodent models are summarized in Table 1.

T2DM animal models

The main characteristics of T2DM are insulin resistance and β cell dysfunction, and defective insulin secretion from β cells. Therefore, animal models of T2DM tend to include models of insulin resistance and/or β cell dysfunction. Most of the T2DM animal models are characterized by the obese phenotype, which reflects the human condition where obesity is closely related to T2DM development^[1]. The T2DM animal models are categorized according to the type of induction mechanism as follows: spontaneously obese models^[1], diet/nutrition induced obesity models^[123,124], non-obese models^[125], genetically induced models of β cell dysfunction^[126], and surgically induced diabetic animal models^[127]. The T2DM rodent models are summarized in Table 2.

DM AND THE NEURAL SYSTEM

DM and central nervous system

Diabetes is significantly related with brain microenvironments and functions. Diabetes is known to largely affect the intensely vascular organs such as kidneys, liver, and brain^[16,18-20,49,50,87,88,95,98,99,128-130]. Brain is the key organ that is involved in hormonal, sensory, and motor regulations so that living organisms can maintain homeostasis *via* the negative feedback system^[46,131]. However, diabetic condition can be a serious chronic stress factor, and its secondary negative effects can exert a bad influence on the

Table 1 Summary of animal models of type 1 diabetes mellitus

Induction	Models	Dose(s) (mg/kg)	Main characteristics	Model uses
Chemicals	Streptozotocin	Rat 35-65 (<i>iv</i> or <i>ip</i>) Mice 100-200 (<i>iv</i> or <i>ip</i>) Hamster 50 (<i>ip</i>) Dog 20-30 (<i>iv</i>) Pig 100-150 (<i>iv</i>) Primates 50-150 (<i>iv</i>)	Hyperglycemia	New formulations of insulin transplantation models
	Alloxan	Rat 40-200 (<i>iv</i> or <i>ip</i>) Mice 50-200 (<i>iv</i> or <i>ip</i>) Rabbit 100-150 (<i>iv</i> or <i>ip</i>) Dog 50-75 (<i>iv</i> or <i>ip</i>)		
Spontaneous autoimmune	Multiple low dose Streptozotocin			Treatments prevent beta cell destructions
	NOD mice BB rats LEW.1AR1/-iddm rats		Beta cell destruction due to an autoimmune process	Understanding genetics of T1DM Understanding mechanism of T1DM Treatments prevent beta cell destruction Treatments manipulate autoimmune process
Genetically induced	AKITA		Beta cell destruction due to ER stress Insulin dependent	New formulations of insulin Transplantation models Treatments to prevent ER stress
Virally-induced	Coxsackie B virus Encephalomyocarditis virus Kilham rat virus		Beta cell destruction induced by viral infection of beta cells	Establish potential role of viruses in the development of T1DM

iv: Intravenous injection; *ip*: Intraperitoneal injection; T1DM: Type 1 diabetes mellitus.

Table 2 Summary of animal model of Type 2 diabetes mellitus

Induction	Model	Main characteristics	Model uses		
Obese models	ob/ob mice db/db mice KK mice KK/Ay mice NZO mice TSOD mice Zucker fatty rat Zucker diabetic fatty rat OLETE rat	Obesity-induced hyperglycemia	Identifying factors involved in obesity-induced diabetes Some models show diabetic complications Treatments to improve beta cell function		
	Non-obese models		GK rat	Hyperglycemia induced by insufficient beta cell function Treatments to improve beta cell function and beta cell survival	
	Diet/nutrition induced obesity		Cohen diabetic rat High fat feeding (mice and rat) Desert gerbil Nile grass rat	Obesity-induced hyperglycemia	Treatments to improve insulin resistance Treatments to improve beta cell function Treatments to prevent diet-induced obesity
			Surgical diabetic animals	VMH lesioned dietary Obese diabetic rat Partially pancreatectomized animals (dog, primate, pig and rats)	Avoid cytotoxic effects of chemical diabetogens on other body organs Resembles human T2DM due to reduced pancreatic islet beta cell mass
	Transgenic/knock-out diabetic animals			Uncoupling protein (UCP1) Knock out mice HiAPP mice	Poor activation of thermogenesis Amyloid deposition in islets

body^[10,46,113]. What is more important is that, since the brain is a very vulnerable and sensitive organ, the duration and severity of DM might result in serious neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease^[10,70,102]. The HPA axis regulates responses to various stress factors, digestion, immune response, mood and emotions, sexuality and energy expenditure/storage^[11,59,104,132-134]. In addition, since the HPA axis is also connected with the autonomic nervous system^[135,136], it is very important when the

brain orders right responses to diverse physiological conditions. If DM persists and/or is increased without any modification, the brain cannot maintain the normal HPA axis regulation, and the HPA axis based on the negative feedback system tends to be highly activated due to uncontrolled DM. However, sometimes exercise-induced stress might influence the beneficial effects of exercise are not observed in certain behavioral test. It is recognized that the amount of psychological stress that an animal encounters determines the degree of

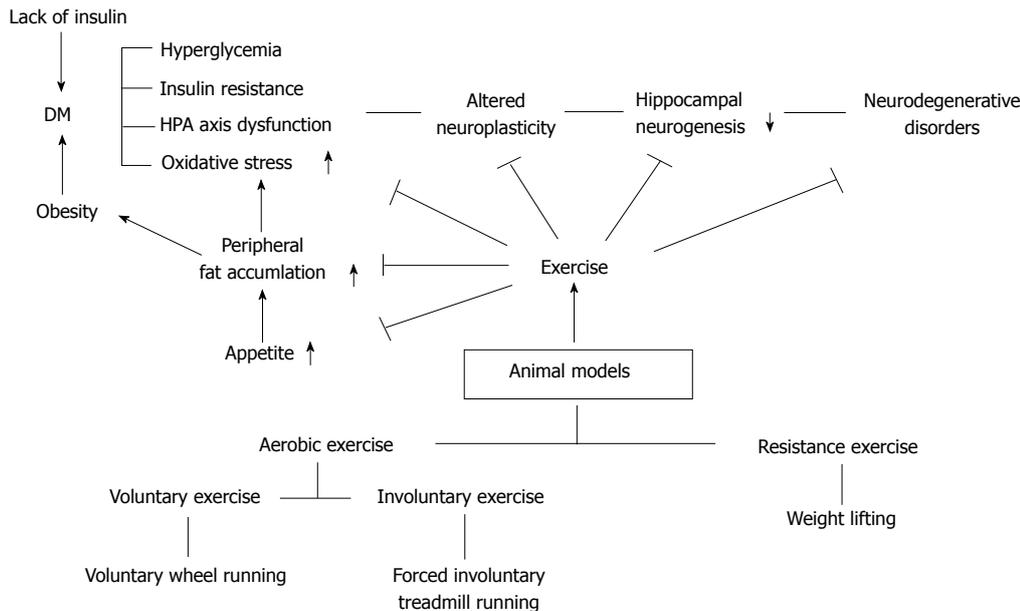


Figure 1 Exercise animal models can separate aerobic voluntary/involuntary exercises and non-aerobic resistance exercise. The exercise can attenuated many neuro-related disease followed DM and obesity. DM can develop many kinds of dysregulation such as hyperglycemia, increasing insulin resistance and HPA axis dysfunction and oxidative stress. Exercise reduces peripheral fat accumulation and appetite in animal models, and it has preventive and therapeutic effects for the many risks to develop obesity and DM. A number of studies about diabetes have been revealed the related mechanisms through exercise animal models. Non-aerobic resistance exercise described in Table 3. DM: Diabetes mellitus; HPA: Hypothalamo-pituitary-adrenal.

response of the HPA axis regulation^[137]. Moreover, it has been reported that animals performing an exercise at the stress-induced physiological and environmental factors can be strongly affected^[59,137-139]. Therefore, there would be enough possibilities to show different behavioral effects under various kinds of stress factors in exercise animal models such as metabolic DM and psychological depression/anxiety disorders. Cayado *et al.*^[137] reported that different training showed different exercise effects at the horse exercise training. Martínez-Mota *et al.*^[138] indicated that the HPA axis response can be different according to sex and age at the exercise animal model. Furthermore, since DM is defined as a chronic systemic inflammatory condition, the disease can contribute to the development of different metabolic disorders. The most significantly affected organs by the chronic inflammatory condition are the vascular converged areas, and thus cardiovascular system is mostly vulnerable and its vascular microenvironment is changed leading to profound damage. Particularly, the occurrence of T2DM is generally characterized by the development of chronic obese condition *via* overnutrition and/or increased hyperphagia^[123,124,133,140,141]. In addition, neuroinflammation and neurodegeneration have been known to be closely related with overnutrition-induced disease and diabetic animal models^[2,4,9,99] (Figure 1).

T2DM is commonly known to be the consequence of chronic obesity and it is usually accompanied by uncontrollable hyperphagia^[142-144]. Many factors contribute to pathologic overeating and mediate feeding behavior in humans and animals, and the most important factor is leptin^[104,145,146]. Leptin, which

is a cytokine originating mainly from white adipose tissue, plays an important role in regulating energy expenditure, food intake, and obesity^[45,71,91,98,104,145,146]. The mechanism by which leptin modulates these hypothalamic neurons involves the binding of leptin to the long form of leptin receptor (Ob-Rb) and subsequent intracellular signaling, initiated by autophosphorylation of Janus kinase 2 (JAK2) and activation of signal transducer and activator of transcription (STAT3). Following the translocation of STAT3 to the nucleus, suppressor of cytokine signaling-3 is activated, exerting feedback inhibition on JAK2. Leptin activation of insulin receptor substrates and the protein kinase B pathway inhibits food intake and modulation of extracellular regulated kinases has been demonstrated to play a role in the control of energy homeostasis^[147]. Obese patients and animals cannot regulate their hedonic appetite except for acceptable daily intake of calories. They have excessive WAT in the body and it secretes leptin in the blood; however, the appetite center does not recognize leptin and shows resistance to leptin. Therefore, leptin administration to obese rats and humans has elicited small effects on fat mass and appetite due to leptin resistance^[2,53,148]. Likewise, many neuropeptides located in hypothalamic nuclei transmit related anorexigenic or orexigenic signals^[104,146]. Furthermore, many kinds of neurotransmitters such as serotonin, dopamine, and norepinephrine participate in regulation of mood, emotions, and appetite^[149]. Particularly, specific serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been introduced and used as medical treatments to reduce food intake of overweight patients^[150-153]. These

drugs have been modified continuously to overcome their side effects or toxicities^[154]; however, chronic administration of SSRIs or SNRIs causes rebound body weight gain in the patients. The phenomenon has been observed for a while; however, the cause was not the patients' psychological drug dependence, and same results have been obtained in many studies performing animal experiments^[155,156]. Since these agents not only influence the appetite center but also the other areas in the brain, the environment of the brain gets affected^[157-159]. Therefore, more specific target regions in the brain and promising regulatory drugs are required. Finally, failure of appetite control can easily lead to T2DM, and then the continuous progression of this metabolic disorder harms the neuroenvironment of the brain and affects learning/memory and cognitive functions^[47,49,85,87,160]. According to the severity of DM, hippocampal neurogenesis in the dentate gyrus is significantly reduced and neuronal plasticity is also negatively influenced through reduction in neurotrophic factors^[31,130,160]. Uncontrolled DM with hyperglycemia can cause serious brain damage; therefore, appropriate therapies that can slow the progression of this disease are needed.

DM and peripheral nervous system

Diabetic neuropathy affecting the peripheral nervous and autonomic nervous systems is the most frequent complication of diabetes. The most common neuropathies are chronic sensorimotor distal polyneuropathy (DPN) and autonomic neuropathies^[161]. Morphologically, DPN is characterized by alterations in peripheral nerve fibers as well as degeneration and regeneration of both myelinated and unmyelinated fibers in humans, decreased axonal diameter of the sciatic nerve and myelin sheath thickness of the sural nerve, and alteration of the cytoskeletal component in dorsal root ganglia of rats^[162-164].

Currently, human life span has dramatically increased due to advances in medical science, and moreover, improving the quality of life has also received attention. Therefore, people are feeling the need to maintain their brain health throughout their life. However, DM poses a threat to the health of people and therefore it has become a problem that needs to be conquered.

EFFECTS OF EXERCISE ON THE BRAIN OF DIABETIC ANIMALS

It is already well known that regular physical activity has a tremendous impact on health and has protective effects against chronic diseases, including heart disease, stroke, hypertension, and DM. Over several decades, many evidences have demonstrated that exercise in human and animal models helps to maintain brain health such as cognitive performance, and it can even protect the central nervous system and improve

learning/memory functions following chronic exercise, both in animal models and humans^[59,61,104,165-171]. In recent years, many exercise and cognition studies have been carried out in adult rodents. These researches have provided insights into the underlying cellular mechanisms^[169,172]. Both voluntary and forced exercise enhanced spatial memory in Morris water maze, Y-maze, T-maze, and radial arm maze test^[65,169]. Particularly, running exercise improved performance in hippocampus-dependent tasks that require limited movement, and there were non-hippocampal dependent benefits from voluntary and forced exercise. Chronic involuntary treadmill exercise in an T2DM animal model (ZDF rats) reduced blood glucose levels, caused cell proliferation and an increase in neuroblasts in the hippocampal dentate gyrus; however, the onset of treadmill exercise in the severe chronic diabetic condition has a limitation in increasing neuroblast differentiation although it increases neural plasticity^[77,80]. Therefore, for achieving effectiveness of treadmill exercise in increasing neuronal differentiation in the hippocampus and for counteracting the negative effect of DM in the brain, the initiation time of exercise during the early stage of DM may be a very critical point to achieve the positive effects of exercise^[77]. Furthermore, Hwang *et al*^[77,173] reported that Cox-2 is very important factor for hippocampal neurogenesis in the T2DM animal exercise models. Griffin *et al*^[167] reported that voluntary exercise also increased volume of the hippocampus resulting in improved search strategies and decreased perseveration once the platform had been moved to a new location. Voluntary exercise results in elevation of levels of factors such as brain-derived neurotrophic factor (BDNF), whose levels increases with aerobic exercise, and enhances hippocampal function^[167].

Interestingly, Burghardt *et al*^[174] studied the behavioral effects of voluntary and involuntary running exercise with a battery of behavioral tests; they investigated the effects of 8 wk of forced treadmill running and voluntary wheel running on behavior measures in the elevated plus maze, open field, social interaction and conditioned freezing paradigms. They found that chronic voluntary running produces behavioral changes in the elevated plus maze and open field; however, chronic treadmill running failed to produce behavioral changes with their running protocol. Changes in opioidergic^[175], serotonergic^[176], GABAergic^[177], and catecholaminergic^[178] systems have also been observed after wheel running. Regular running exercise is closely associated with food preference and appetite depending on the volitional wheel running and involuntary treadmill exercise. Recently, attention has been paid to various causes of food preference and consumption according to a wide range of conditions for overcoming the obese and DM conditions^[179]. Diet composition may lead to changes in neuropeptides within brain nuclei regulating energy metabolism. Dietary manipulation has been thought to influence energy expenditure *via* changes in

central neuropeptide activity. Many studies report that medicines such as morphine, fenfluramine influence the neuro-regulatory systems and exercise can modify palatability in animals^[175]. Blundell *et al*^[37] asserted that changes in dietary preferences could be due to alterations in the hedonic properties of the food as a result of exercise in rodent models. Shin *et al*^[144] also indicated a possibility that treadmill exercise in animals inhibits diabetes-induced increment of the desire for food. Hormonal (leptin and insulin) and nutrient signals from the periphery are mainly integrated in the hypothalamus, and multiple factors regulate food intake. AMP-activated protein kinase (AMPK) is the downstream component of a kinase cascade that acts as a sensor of cellular energy charge, being activated by rising AMP coupled with falling ATP^[180]. Although the effects of AMPK on desire for food are still controversial, exercise may contribute to appetite suppressive actions in the hypothalamus due to the effects of leptin and in different causes in the rodent model^[147,179-182]. As mentioned above, alterations in opioid or inhibitory neurotransmission systems in both limbic and brainstem areas could be implicated, including the nucleus accumbens^[183]. Multiple mechanisms of action in the brain could be responsible for this behavioral difference and lack of gross metabolic difference^[171]. In humans, texture, temperature, color, and appearance all play a role in food acceptance^[184,185]; however, animals exhibit a wide range of food preferences and animal studies can eliminate the points of dispute in human studies. In addition, an important element in the study of effects of exercise on food preference is sex differences^[171,175,179]. Sex differences exist such that female rats tend to prefer carbohydrates over other macronutrients following exercise^[134,175]. Unfortunately, there is still no clear evidence on the effect of exercise on macronutrient or carbohydrate selection in different sexes in animal or human studies. Therefore, further research for assessing the sex differences in food preference after exercise is needed.

Chronic inflammation and increased oxidative stress are observed in the animals showing insulin resistance following diet-induced obesity^[36,44,45,62,131,186,187]. Indeed, since the brain tissue is highly sensitive to chronic inflammation and oxidative stress due to its high oxygen consumption, iron and lipid contents, and low activity of antioxidant defenses^[102,188], energy metabolism impairment and oxidative stress are important events that have been related to the pathogenesis of diseases affecting the central nervous system^[47,180]. Exercise has been known to decrease chronic systemic inflammatory response, show antioxidant effects and positive effects on synaptic plasticity in the obese and/or diabetic rodents^[55,60]. In the T1DM animal model, significant inflammatory responses are found and they showed different action in a time-dependent manner^[113]. These responses induced by DM lead to mitochondrial dysfunction, which can progress to various pathologies such as neurodegenerative diseases (dementia,

Alzheimer's disease, Parkinson's disease)^[33,34,47,61]. Both T2DM and neurodegenerative diseases are associated with impaired glucose tolerance and cognitive decline in the human and animal studies, and insulin resistance and subsequent hyperinsulinaemia have been found to increase the risk of Alzheimer's disease and promote decline in memory and cognitive dysfunction^[3,34,61,133,189]. Regular exercise and dietary restriction can attenuate the progression of metabolic and neurodegenerative disorders^[4,5,67,190]. Exercise (particularly vigorous aerobic exercise)^[111,167,191-193] and energy restriction (caloric restriction and intermittent fasting)^[143,194,195] can result in striking improvements in glucose and lipid metabolism, and can eliminate the need for medications. Exercise and dietary energy restriction activate a wide range of adaptive cellular responses in the peripheral organs (muscle, liver) and the brain, resulting in improved bioenergetics and brain function, and resistance to neurodegenerative disorders.

As mentioned previously, the causes of DM belong to different metabolic conditions and can show diverse pathologic phenotypes in a time-dependent manner^[113]. This review mainly focused on the changes in the brain caused by DM and exercise; however, changes in peripheral neuropeptides and organs are also significant. Adiposity, chronic inflammatory response, activation of oxidative stress, dysfunction of pancreatic islets, insulin and leptin resistance, dysfunction of the negative feedback mechanisms, and appetite disturbance constantly affect brain homeostasis. Indeed, exercise has been thought to attenuate brain damage caused by these risk factors; however, exercise during the early stage of diabetes is considered to be a critical factor for preserving brain function^[10,80]. The risk factors listed above can be therapeutic targets to treat and ameliorate DM; thus, refinements using various animal exercise models can give new insights into the treatment of DM.

It is well accepted that physical activity by contracting skeletal muscles (resistance exercise) secretes enhanced levels of myokines which have a beneficial endocrine effect on other organs, presenting novel targets for the treatment of metabolic diseases and T2DM^[70-72,94]. Pedersen hypothesized that physical inactivity leads to T2DM, depression, dementia, cancers, cardiovascular diseases, and asserted that skeletal muscle should be considered as an endocrine organ^[70]. Cytokines and other peptides that are produced, expressed, and released by muscle fibers and exert paracrine or endocrine effects should be classified as myokines. Actually, since skeletal muscle is the largest organ in the human body, skeletal muscle should receive attention for identifying its new multiple functions in metabolic disorders and T2DM. Skeletal muscle has the capacity to express several myokines including IL-6, IL-8, IL-15, BDNF, FGF21, MCP-1, vascular endothelial growth factor, leukemia inhibitory factor, Irisin, and ANGPTL4^[71]. IL-6 was discovered as a myokine because of the observation that it increases

Table 3 Exercise animal models on brain function

Exercise type	Method	Measurement	Note ¹	Note ²
Aerobic exercise	Voluntary running wheel exercise	Freely access to running wheel Exercise strength can be measured <i>via</i> digital counter. The running wheel was rotated by animal effort		Cognitive performance Neurogenesis in subgranular zone or subventricular zone Improvements of learning and memory
	Involuntary treadmill exercise	Enforced running exercise Regularly enforced running exercise is enforced with constant speed on a motorized treadmill		Neurophysiological development Relationship between Brain and Stress axis
	Forced swimming	Animals are forced to swim in an acrylic glass cylinder filled with water	This test is used to see a rodent's response to the threat of drowning whose result has been interpreted as measuring susceptibility to negative mood. It is commonly used to measure the effectiveness of antidepressants	Feeding behavior
Non-aerobic resistance exercise	Weight lifting	Kondziela's inverted screen test	The inverted screen is a 43 cm square of wire mesh consisting of 12 mm squares of 1 mm diameter wire	Cognition Neuronal plasticity changes
		Weights test	Seven weights constitute the apparatus Ranging from 20 to 98 g	Anti-inflammatory response in brain
		Grip strength test	Forelimb grip strength is accessed using a digital Grip Strength Meter	Neurogenesis in subgranular zone and subventricular zone

¹Principal; ²Uses.

up to 100-fold in the circulation during exercise. In particular, the identification of IL-6 production by skeletal muscle during physical exercise generated renewed interest in the metabolic role of IL-6 since it created a paradox^[70]. IL-6 can also alter brain function after peripheral administration, moreover, some myokines might be able to cross the blood-brain barrier^[196,197]. IL-6 is significantly produced and released in the post exercise period when insulin action is increased; on the other hand, IL-6 has also been associated with obesity and reduced insulin action. However, many researches during the past decade have reported that in response to muscle contraction, both type 1 and type 2 muscle fibers express the myokine IL-6, which subsequently exerts its effects locally and systemically in several organs^[70-72]. Within skeletal muscle, IL-6 acts to signal *via* AMPK and/or PI3-kinase to enhance glucose uptake and fat oxidation. In addition, muscular derived IL-6 mediates anti-inflammatory responses^[70].

A few researches on the relationship between myokines and the brain in animal models have just been published, and the effects of skeletal muscle derived myokines on brain function must be plausible enough directly and/or indirectly. Recently, Dun *et al.*^[198] reported that myokine Irisin was detected in three types of cells; skeletal muscle cells, cardiomyocytes, and Purkinje cells of the cerebellum. Moreover, they reported that Irisin not only mediates the animal's movements but also regulates adipose tissue thermogenesis by neurons in the caudal ventrolateral medulla and rostral ventrolateral medulla that are an integral component of the medullary sympathetic circuitry and these neurons project their axons to spinal sympathetic premotor neurons^[198]. Similarly, it is known that resistance exercise improves body and brain bioenergetics for PD

risk reduction^[4], insulin and leptin signaling in obese rats^[2,45,82,104,199], and exerts antidepressant-like effects *via* improving the impaired neuroplasticity^[101,200]. Aerobic exercise and non-aerobic resistance exercise described in the Table 3.

Evidences of positive effects of resistance exercise on brain health in T2DM for therapeutic purposes with other aerobic exercises and pharmacologic treatments have been reported recently, and further studies on the mechanisms of treatment according to the severity of DM are needed.

CONCLUSION

It is confirmed that exercise is an incredible therapeutic option for treating DM patients. Animal exercise models are significant methods to study the network between central and peripheral organs. Brain is an extremely sensitive and soft tissue that can be damaged due to chronic insulin resistance, hyperglycemia, and chronic inflammation; however, various kinds of exercise can attenuate the brain damage and delay neurodegeneration caused by the risk factors. Many diabetic experimental animals with a genetic background and nutrition induced diabetic animals can be used in various DM studies; however, many physiopathologic conditions should be considered, and researchers should choose the animal models after giving careful consideration. Many aerobic running exercises and resistance skeletal muscle exercises have been performed recently in various animal models to study their therapeutic effect on brain function; however, more careful considerations reflecting the clinical conditions should be added in the animal models. Furthermore, it is important to study the therapeutic effects of exercise on brain health during

the stages of DM in animal models; however, dramatic effects of more prospective methods for maintaining brain health during DM seem to be achieved through development of various combinations of animal models in the pre-diabetic condition. A number of target signals from the exercise studies can also be the candidates for development of pharmacologic medicines.

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