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REVIEW ARTICLE

Neuroprotective effects of exercise in rodent models of memory deficit and Alzheimer's

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Abstract
Alzheimer's disease (AD) is a fastest growing neurodegenerative condition with no standard treatment. There are growing evidence about the beneficial effects of exercise in brain health promotion and slowing the cognitive decline. The aim of this study was to review the protective mechanisms of treadmill exercise in different models of rodent memory deficits. Online literature database, including PubMed-Medline, Scopus, Google scholar were searched from 2003 till 2017. Original article with English language were chosen according to following key words in the title: (exercise OR physical activity) AND (memory OR learning). Ninety studies were finally included in the qualitative synthesis. The results of these studies showed the protective effects of exercise on AD induced neurodegerative and neuroinflammatory process. Neuroperotective effects of exercise on the hippocampus seem to be increasing in immediate-early gene c-Fos expression in dentate gyrus; enhancing the Wnt3 expression and inhibiting glycogen synthase kinase-3β expression; increasing the 5-bro-mo-2'-deoxyridine-positive and doublecortin-positive cells (dentate gyrus); increasing the level of astrocytes glial fibrillary acidic protein and decrease in S100B protein, increasing in blood brain barrier integrity; prevention of oxidative stress injury, inducing morphological changes in astrocytes in the stratum radiatum of cornu ammonis 1(CA1) area; increase in cell proliferation and suppress apoptosis in dentate gyrus; increase in brain-derived neurotrophic factor and tropomyosin receptor kinase B expressions; enhancing the glycogen levels and normalizing the monocarboxylate transporter 2 expression.

Keywords Alzheimer' disease · Neurodegeneration · Exercise · Memory · Learning · Animal models

Introduction

During the past century the average of life expectancy has been increased due to health improvement and communicable and infectious disease prevention. Aging and its related diseases, especially Alzheimer's has been proposed as a new challenge of world organization systems. Therefore, many investigations have been undertaken to develop therapeutic strategies for slowing down the memory deficit and cognition decline process of aging (Bishop et al. 2010). Moreover, changes in lifestyle and physical inactivity increased incidence of many chronic non-communicable diseases, including diabetes and metabolic syndrome, which disturb the healthy aging process and increase the risk of Alzheimer disease (AD) (Lee et al. 2012). These pathological statuses may augment the normal aging process of structural and physiological changes in the brain.

The result of many animal models, preclinical and clinical studies have proposed different etiology for late-onset AD. Epigenetic factors and oxidative stress, reduction in basal autophagy, mitochondrial dysfunction, vascular disorders, chronic low grade neuroinflammation and insulin resistance are the proposed etiological mechanisms prior to amyloid-β (Aβ) and tau deposition in AD pathology (Bishop et al. 2010). Among them chronic neuroinflammation is the most important mechanism which augments aging neurodegeneration process (Nazem et al. 2015). Therefore a healing strategy for prevention and curing AD should target neuroinflammation as the main cause of neurodegeneration. There are also close correlation between insulin-like growth factor (IGF-1) and

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brain-derived neurotrophic factor (BDNF) activity as the neurotrophic signaling pathways of learning and memory function improvement. Consequently, these molecular pathways are being evaluated in neuroprotective procedures.

Physical exercise and lifestyle modification as an effective and natural healing process have been taken into consideration in many age related disorders especially neurodegenerative diseases (Cassilhas et al. 2016). Moreover, regular exercise like a miracle drug has many beneficial effects on the body and protects against cancer, cardiovascular and other chronic non-communicable diseases which are accompanied with cognitive decline (Gholamnezhad et al. 2014; Pimlott 2010). World Health Organization guideline regarding physical activity is "adults should do at least 150 min a week of moderate intensity, or 75 min a week of vigorous intensity aerobic physical activity, or an equivalent combination of moderate and vigorous intensity aerobic activity" (Global Recommendations on Physical Activity for Health. 2010). There are growing evidence about the beneficial effects of exercise in brain health promotion and slowing the cognitive decline according to human studies. These documents are not limited to normal or disease status and findings are similar in young, adult and geriatric population (Benedict et al. 2013; Chaddock et al. 2010; Duzel et al. 2016) . In addition, many animal studies (most of them on rodents) have been undertaken to elucidate the cellular and molecular mechanisms of these beneficial effects. The positive effects of physical activity on spatial learning and memory and its protective effects on neurodegenerative disease has been explained by different mechanisms which are relying on an increase in hippocampal neurogenesis, neural plasticity, neurotrophins, angiogenesis and, cell proliferation (Bishop et al. 2010; Johansen-Berg and Duzel 2016).

The impact of different load of exercise training on the impairment of cognitive processes may vary based on the nature, severity and time lag between exercises. Intensive exercise without adequate recovery (overtraining) would lead to stress overload, which might cause sign and symptom of cognitive disturbance due to induction of oxidative stress, elevation of stress hormones, immunosuppression and inflammation. While, moderate and regular exercise as a non-invasive method can enhance memory and learning functions (Clark and Mach 2016). These effects are associated with cellular and molecular changes in brain structure. Increase of endorphins (Dinas et al. 2011), catecholamines (Skriver et al. 2014) and neurotropic factors such as BDNF (Voss et al. 2013), as well as the reduction of inflammatory cytokines (Chennaoui et al. 2015) and correction of oxidative damage (Stranahan et al. 2012) are effective factors that improve memory after exercise. Moderate intensity exercise reduces the risk of chronic diseases and also increases neurotrophin levels that lead to increase of neuronal survival (Stranahan et al. 2012). Also moderate exercise can increase the neurogenesis in dentate gyrus of hippocampus that lead to memory and learning improvement (Kim et al. 2010). In addition, effects of different loads (mild, moderate or severe) and durations (acute or chronic) of exercise training on long term memory have been not fully elucidated. According to systematic review of human studies finding, cardiovascular acute exercise has more effect on long term memory than chronic exercise. Acute exercise potentiate molecular mechanism related to both encoding and consolidation of new information. While, chronic exercise mostly affects the signal transduction mechanism of memory processing and has a small effect on memory (Roig et al. 2013). However, both human and rodent studies provide several evidences which supports the effect of long term exercise on memory and cognition. The improving effect of chronic exercise on molecular pathways, including; mitogen-activated protein kinase (MAPK), NMDA- receptor, BDNF, cAMP response element binding (CREB, long-term neuronal plasticity critical factor) as well as behavioral hippocampal-related memory tasks support the beneficial effect of chronic exercise on long term memory (Gomez-Pinilla and Hillman 2013; Cassilhas et al. 2016).

The aim of this review was to discuss systematically the protective effects of aerobic treadmill exercise on neurodegeneration and memory deficit, which has been induced in rodent animal models or aged ones as well as normal animals.

Methodology

Online literature database, including PubMed-Medline, Scopus, Google scholar were searched from 2003 till 2017. Original articles with English language were chosen according to following key words in the title: (exercise OR physical activity) AND (memory OR learning). Review articles, abstract in congress and symposium, human studies, other exercise than treadmill exercise or combination therapy, and motor memory and learning were excluded (Fig. 1).

Memory enhancing function of exercise in normal rodent

The normal aging process may decrease neurogenesis and increase apoptosis in hippocampus, which are associated with memory and cognitive deficit in the geriatric population. In addition, aging is associated with neurodegenerative disorders that may accelerate memory or learning performance decline (Kim et al. 2010; Lister and Barnes 2009).

The beneficial effect of exercise on memory function, hippocampal neurogenesis and synaptic plasticity has been shown to be related to changes in circadian rhythm. Treadmill exercise training (V=8 m/min, 30 min/day for 7

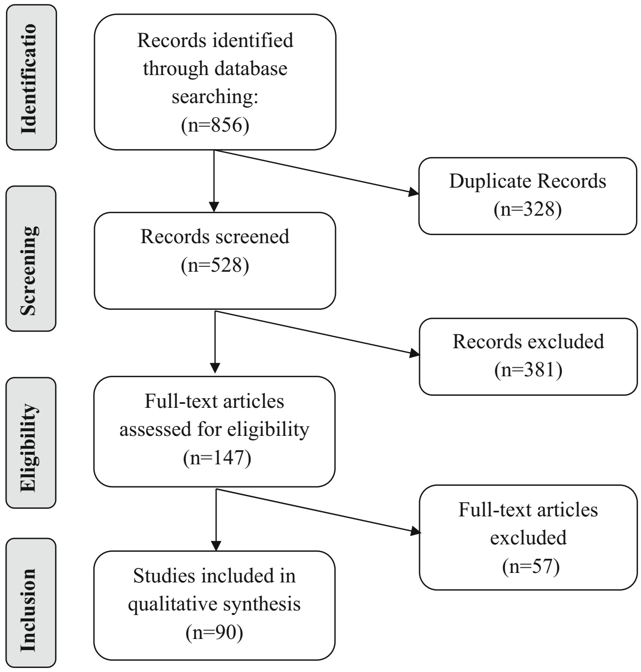

Fig. 1 Flow chart of the number of studies identified and included in systematic review

weeks) of mice during the day had more effect on short-term memory improvement (step-down avoidance test), spatial learning capacity (8-arm maze test), elevation of synaptic plasticity-associated protein expression and neurogenesis in hippocampus compared to training mice in the evening (Hwang et al. 2016).

Physical activity is accompanied with better outcome of behavioral and cognitive tasks and delay onset of memory decline. Several studies have been done to reveal molecular mechanisms and related pathways of these effects (Cardoso et al. 2017). It has been shown that treadmill exercise training (V=15 m/min, 30 min/day for 4 weeks) improves memory in middle-aged rats (18 months old) and cognitive performance (aversive memory by avoidance test). In these aged rats, exercise decreased extracellular signal-regulated protein kinase (ERK) and p38 mitogen-activated protein kinase (p38) in hippocampus. These extracellular signaling pathways are related to inflammation, therefore exercise may ameliorate age-related memory impairment by a decrease in neuroinflammation and cell death (Cardoso et al. 2017). It was indicated that mild-intensity treadmill running for a short time (V=10 m/min, 4–6 min /day for 5 weeks) ameliorates long-term spatial learning and memory (morris water-maze or MWM) in aging rats (24 months), while short-term memory (step down avoidance test) was not improved significantly. Short bouts of treadmill exercise increased hippocampal plasticity by activation of serine/threonine protein kinase (AKT), cAMP response element binding (CREB) and signalling in hippocampus, also increased oxygen consumption in soleus and heart muscles (Aguiar et al. 2011). Forced treadmill exercise increased the level of neurotrophins in the basal forebrain and improved spatial learning. Mild-intensity treadmill running (V=8 m/min, 15 min /day for 7 weeks) also enhanced spatial learning and memory in the aged rat (25 months) by shortening the latency and distance in MWM test, while the neurotrophin levels in the basal forebrain was not changed significantly compare to sedentary animals (Albeck et al. 2006).

Exercise may regulate the enzymatic process in neural cell membrane. It has been demonstrated that treadmill exercise (V=5 m/min speed increment until exhaustion, 20 min/day for 4 weeks) prevents memory loss in aged rats (22 months) by enhancing the activities of some enzymes such as sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase) and acetylcholinesterase (AChE) as well as ameliorating working and spatial memory deficit in aged rats (22 months) which was evaluated by MWM test. These enzymatic processes play important roles in neuronal transmission, which memory processing needs to regulate them (Vanzella et al. 2017).

In addition, exercise may improve cerebral cortex structural changes which are related to the agining process. Wang et al. reported that long-term treadmill exercise (V=20 m/min, 20 min/day) might have beneficial effects on spatial learning and memory function in aged male and female rats depending on animals age and duration of exercise training. After 4 months exercise training MWM test results of spatial memory in 18 month old female animals, but not for the male rat was improved significantly compared to non-trained animals. While after 14 month training those results were reversed for 28 month old male and female rats and the escape latencies was improved in male exercised rats. Moreover, exercise increased the stereological parameters of cortical capillaries such as total volume and total surface area in aged male and female, while enhanced total length of cortical capillaries only in aged male rats (Wang et al. 2015). Moreover, it was reported that 12 weeks of voluntary running improved cognitive function in aged mice (22 months). Voluntary exercise decreased memory deficit of the older animals more than younger rats, which was indicated by the improvement of the MWM test results and an increase in neurogenesis and the restoration of presynaptic density in the hippocampus (Siette et al. 2013). It has been shown that aging process induces memory deficit by enhancing apoptosis and decreasing neurogenesis in the dentate gyrus of the hippocampus and poor performance in step-down avoidance and radial arm maze (RAM) task. In aged rats (24 months) treadmill exercise (V=5 m/min, 30 min/day for 6 weeks) increases neurogenesis and inhibits apoptosis in the hippocampus and improve the performance of behavioral task, so prevents age-related memory losses (Kim et al. 2010).

It was reported that treadmill exercise (V=9-13 m/min, 30 min/day for 12 weeks) improved antioxidant status as well as decreased the levels of reactive oxygen species (ROS) in striatum, prefrontal cortex and hippocampus which are related to memory. Also, exercise reverse long-term memory impairment associated with aging (9 months) in the object recognition and inhibitory avoidance tasks (Flores et al. 2014).

Treadmill exercise (V=20 m/min, 20 min/day for 4 months) might have an effective role on spatial learning functions in middle-aged female rats (14 months). Exercise increased the total length and surface area of the capillaries in the cortex and these changes could be one of the structural bases for alleviation in spatial learning capacity following exercise in middle-aged female rats (Huang et al. 2013). Chae et al. reported that moderate treadmill exercise (V=18-20 m/min, 50 min/day for 8 weeks) could improve learning and memory dysfunction in D-Galactose induced aged rat (50 mg/kg for 8 weeks). Results indicated that exercise increased the level of nerve growth factor (NGF) and activated phosphatidylinositol 3-kinase (PI3K)-AKT pathway, so blocked apoptosis in the hippocampus of aged rat (Chae and Kim 2009). In another study treadmill exercise (V=9.5 m/min, 20 min/day for 2 weeks) alleviates aging-related aversive memory impairment in 20 months old rat. These results suggest that exercise improves the performance in inhibitory avoidance task and decline pro-inflammatory marker specially tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), and Nuclear factor-kappa B (NFκB) as well as increase the levels of histone H4 acetylation and pro-inhibitory cytokine included interleukin 4 (IL-4) in hippocampus of aged rat (1 h, 18 h, 3 days or 7 days after the last session of treadmill exercise) (Lovatel et al. 2013).

Table 1 summarizes the neuroperotective effects of exercise in normal aged rodents.

Memory enhancing function of exercise in different rodent models of memory deficiency

The effect of aerobic treadmill exercise on *in vivo* models of Alzheimer's disease has been shown. The basis of most of them is on Aβ deposition, neuroinflammation and, neurodegeneration, which may have been induced by some drugs, toxins, vascular disorders and stress (Nazem et al. 2015; Puzzo et al. 2015).

Effects of exercise in neurotoxin-induced memory deficiency

Amyloid beta induced memory deficiency

Aβ peptide is considered as an important factor in the production and progress of AD. ICV injection of Aβ causes impairment of brain glucose and energy metabolism through desensitization of neuronal insulin receptors and is used for the animal model of AD (Dao et al. 2013; Kim et al. 2015b).Treadmill exercise (V=15 m/min, 60 min/day for 4 weeks) prevents learning and short-term memory impairment induced by ICV infusion of Aβ (250 pmol/day Aβ1–42 peptides) as a rat model of AD. Aβ infusion increased the animals' errors in radial arm water maze (RAWM) test, decreased BDNF and phosphorylated calcium calmodulin dependent protein kinase II (p-CaMKII) and inhibited long-term potentiation (E-LTP) in CA1 area. While moderate treadmill exercise reduced the animals' errors in RAWM test and plays a neuroprotective role in this AD model and increased BDNF and p-CaMKII levels, activated E-LTP and inhibited the up regulation of calcineurin during E-LTP (Dao et al. 2013). Mild treadmill exercise (V=8 m/min, 30 min/day for 4 weeks) also ameliorates short-term memory impairment induced by ICV injection of Aβ 25-35 (1.5 mg/kg) in rats. After the last session of treadmill exercise short-term memory was evaluated by a step-through avoidance task. The result of this study indicated that treadmill exercise enhanced neurogenesis and expressions of BDNF and trkB in the hippocampal dentate gyrus, so is useful for improving symptoms of Alzheimer's disease (Kim et al. 2015b). Therefore, the beneficial effect of exercise on ICV infusion of Aβ could be mediated by following mechanisms. Exercise enhances neurogenesis and expressions of BDNF and trkB in the hippocampal dentate gyrus, increases BDNF and p-CaMKII levels and activates E-LTP while it inhibits up regulation of calcineurin during E-LTP.

Ethanol induced memory deficiency

Chronic ethanol abuse causes many disorders in the brain, especially hippocampus. Alcohol exposure induces fetal alcohol spectrum disorder and learning and memory problems and can affect academic and social functioning throughout life (Christie et al. 2005; Hashemi Nosrat Abadi et al. 2013). Exercise could increase LTP induction and BDNF levels in hippocampal dentate gyrus in ethanol-induced memory deficiency animal model. It had been shown that voluntary exercise (for five consecutive days) improves impairment of spatial memory and LTP in prenatal ethanol-exposed rats (35.5% ethanol-derived calories). This study suggests that voluntary exercise alleviates behavioral performance in MWM and increases the LTP induction and BDNF levels in hippocampal dentate gyrus, thus can ameliorate ethanol-induced deficits and improve learning and memory ability (Christie et al. 2005).

In another study treadmill exercise (V=17 m/min, 60 min/day for 4 weeks) alleviates impairment of spatial learning and memory induced by ethanol (4 g/kg, 20% v/v for 4 weeks) in adult rats. According to the result of this study treadmill running reduced the impairment of performance in the MWM task (2 weeks after the ethanol withdrawal), so could improve or prevent these deficits that cause by administration of ethanol (Hashemi Nosrat Abadi et al. 2013).

Table 1 Neuroperotective effects of exercise in normal aged rodents

Experimental model	Exercise protocol	Molecular and structural effect	Behavioral test and effect	Reference
Aged mice/circadian rhythm	V=8 m/min, 30 min/ day for 7 weeks	↑synaptic plasticity-associated protein expression and neurogenesis in hippocampus	↑short-term (step-down avoidance test); spatial long-term memory (8-arm maze test)	(Hwang et al. 2016)
Middle-aged male rats (18 months old)	V=15 m/min, 30min/ day for 4 weeks	↓ERK and p38 in hippocampus	↑aversive memory (avoidance test)	(Cardoso et al. 2017)
Aged female rat (24 months)	V=10 m/min, 4–6 min/ day for 5 weeks	↑hippocampal plasticity by activation of AKT, CREB and BDNF signalling, ↑oxygen consumption in soleus and heart muscles	long-term spatial long-term memory (MWM); no change in short-term memory (step down avoidance test)	(Aguiar et al. 2011)
Aged rat (25 months, male Brown Norway/Fisher 344)	V=8 m/min, 15 min/ day for 7 weeks	↑level of neurotrophins in the basal forebrain	↑spatial long-term memory (MWM test)	(Albeck et al. 2006)
Aged male rat (22 months)	V=5m/min incremental speed until exhaustion, 20min/day for 4weeks	↑Na+, K+, ATPase, AChE	↑working (short-term) and spatial (long-term) memory (MWM test)	(Vanzella et al. 2017)
Aged male and female rat (18 or 28 month)	V=20m/min, 20min/ day for 14 months	↑the physiologic parameters of cortical capillaries (Wang et al. 2015, 2015)	↑spatial memory in 18M female not in male after 4 m training and the reversed result after 14 M training (MWM test)	Wang et al. 2015
Aged female rat (20-month-old)	12 weeks of voluntary running	↑neurogenesis and restored presynaptic density	↑MWM test results	(Siette et al. 2013)
aged	V=5 m/min, 30 min/ day for 6 weeks	↑neurogenesis and ↓apoptosis	↑step-down avoidance and radial arm maze results	(Kim et al. 2010)
Aged male rat (9 months)	V=9-13 m/min, 30 min/ day for 12 weeks	improved antioxidant status	↑recognition long-term memory (object recognition test) and aversive long term memory (inhibitory avoidance test)	(Flores et al. 2014)
Middle aged (14-month-old female/male) rats	V=20 m/min, 20 min/ day for 4 months	↑total length and surface area of the capillaries in the cortex	-	Huang et al. 2013
D-Galactose induced aged rat	V=18-20 m/min, 50 min/ day for 8 weeks	↑NGF, PI3K-AKT	-	Chae and Kim 2009
Male rats (3 and 20-months)	V=9.5 m/min, 20 min/ day for 2 weeks	↓TNF-α, IL-1β and NFκB; ↑histone H4 acetylation and IL-4	↑memory (step-down avoidance test)	Lovatel et al. 2013

↑ improvement or increase; ↓: decrease; *ERK*, extracellular signal-regulated protein kinase; *MWM*, morris water maze; *AKT*, serine/threonine protein kinase; *CREB*, cAMP response element binding; *BDNF*, brain-derived neurotrophic factor; *AChE*, acetylcholinesterase; *M*, month; *NGF*, nerve growth factor; *PI3K*, activated phosphatidylinositol 3-kinase; *TNF-α*, tumor necrosis factor-α; *IL-1β*, interleukin 1β; *NFκB*, Nuclear factor-kappa B

Lipopolysaccharide-induced neuroinflammation

Chronic neuroinflammation plays an important role in the pathogenesis and neurodegenerative process of AD (Nazem et al. 2015). Increase in pro- and inflammatory mediators (IL-6, IL-1β, TNF-α, reactive oxygen species and nitrogen) are resulting in a hyperactive and dystrophic microglia and dysfunctional phagocytosis. These changes would lead to more and more neurotoxic inflammatory response, elevation of amyloid precursor protein synthesis and neurodegeneration (Krstic and Knuesel 2013).

Neuroinflammation induced by lipopolysaccharide (LPS) administration is a common animal model of AD. Memory and learning deficit of chronic central LPS infusion is very similar to AD cognitive decline (Lee et al. 2008). Moreover the systemic endotoxin administration would cause partial hippocampal damage (context-object discrimination impairment) (Anaeigoudari et al. 2015b; Czerniawski et al. 2015). LPS stimulates microglia activation by binding to membrane CD14 and interacting with toll-like receptor-4. This process will lead to the release of proinflammatory cytokine (interleukin (IL)-1, IL-6, IL-12 and tumour necrosis alpha (TNF-α)), anti-inflammatory cytokines (IL-10 and transforming growth factor (TGF-β)), chemokines (chemokine(C-C motif) ligand (CCL)2, CCL 5, chemokine (C-X-C motif) ligand (CXCL8)) and proteins of the complement system (C3, C3a) in the CNS (Abareshi et al. 2016; Bargi et al. 2017; Kim et al. 2015a; Loprinzi et al. 2017; Nazem et al. 2015; Wu et al. 2007). LPS also enhanced malondialdehyde (MDA) and nitric oxide (NO) metabolites concentrations and decreased thiol content, superoxide dismutase (SOD) and catalase (CAT) in hippocampus and cortex (Abareshi et al. 2016; Anaeigoudari et al. 2015a; Anaeigoudari et al. 2016a, b; Bargi et al. 2017). It has been reported that neuroinflammation induced by LPS has a roles in learning and memory impairments. In the MWM test, escape latency and traveled path and in passive avoidance (PA) test, latency to enter the dark compartment were higher in LPS group than the control group. Also the amplitude and slope of field excitatory post synaptic potential (fEPSP) decreased in the LPS group (Anaeigoudari et al. 2015b; Anaeigoudari et al. 2016a, b).

It has been demonstrated that treadmill exercise (V=10 m/min, 60 min/day for 5 weeks) ameliorates LPS-induced (1 mg/kg; intraperitoneal (i.p.)) spatial learning and memory impairment that was evaluated by MWM test. These results showed that running exercise enhanced BDNF and TrkB expression and counteracts inflammatory (Two days after the last LPS injection) effects of LPS on neurogenesis, thus improved learning and memory (Wu et al. 2007). Moreover, forced treadmill exercise (V=10 m/min, 30 min/day for 6 weeks) improved impairment of short-term memory that induced by administration of LPS. In this study, treadmill running increased the latency time in step-down avoidance task (38 days after beginning the treadmill) and inhibited DCX expression and enhanced neuronal nuclear antigen (NeuN) expression and evaluated neuronal maturation in the hippocampus (immediately after determining the latency time of the step-down avoidance task.), so improves memory impairment after LPS-induced brain inflammation (Kim et al. 2013).

It was shown that mild and moderate intensity of treadmill exercise (V=8-14 m/min, 30 min/day for 4 weeks) improved short-term memory in the rat pups born from maternal that had been exposed to LPS (0.15 mg/kg; i.p.) injection. These results suggest that both mild and moderate intensity of treadmill exercise increased latency in the step-down avoidance task and enhanced cell proliferation and neurogenesis in the hippocampal dentate gyrus through increasing BDNF and TrkB expression (immediately after the completion of the step-down avoidance task). Therefore, exercise could improve short-term memory impairment in the rat pups (Kim et al. 2015a). In addition, treadmill exercise (V=8 m/min, 30 min/day for 4 weeks) ameliorates motor and short-term memory dysfunctions in cerebral palsy rats, which have been induced by intracervical injection of LPS (0.15-mg/kg). This study suggests that treadmill running increases the latency in Step-down avoidance task and activates PI3K-AKT pathway and increases synaptic plasticity and neurogenesis in the hippocampal dentate gyrus (Jung and Kim 2017).

Taken together beneficial effect of exercise on LPS induced neuroinflammation and memory and cognitive decline may be through enhancement of BDNF, TrkB, NeuN expression; increase in cell proliferation, synaptic plasticity and neurogenesis of the hippocampal dentate gyrus; activation of the PI3K-AKT pathway and inhibition of DCX expression.

Morphine induced memory deficiency

Morphine is useful for the treatment of chronic pain, and also has effects on brain regions that involved in cognitive functions such as learning and memory. Chronic morphine administration enhances oxidative stress and can damage neurons, so induce impairment of learning and memory (Ghafari and Golalipour 2014; Zhou et al. 2011). Exercise could block cognitive and behavioral impairments of morphine use, activate neurotransmitters systems (dopaminergic, serotonergic and glutamatergic) and increase the release of endorphin (Archer et al. 2017; Meeusen 2005).

Zarrinkalam et al. study showed that regular treadmill exercise (V=10 m/min, 60 min/day for 10 weeks) improves impairment of spatial learning and memory that was evaluated by MWM (after completion of exercise) in rats after morphine (0.1-0.4 mg/ml added to the drinking water) dependence (Zarrinkalam et al. 2016). It has been also shown that mild and severe treadmill exercise (V=10 m/min for mild and 22 m/

min for severe, 30 min/day for 4 weeks) alleviate spatial memory impairment induced by injection of morphine (10 mg/kg, bi-daily doses at 12 h intervals) in female rats. Results suggested that mild treadmill exercise decreased the anxiety levels that was evaluated by elevated plus maze (EPM) test and severe treadmill exercise increased spatial memory in object location memory task (OLMT). These study findings showed that forced exercise could reduce the cognitive and behavioral effects of injection of morphine (Ghodrati-Jaldbakhan et al. 2017).

Scopolamine induced memory deficiency

Degeneration of cholinergic neurons in hippocampus and cortex is one of the probable events in AD pathogenesis. Scopolamine is a non-selective muscarinic cholinergic receptor antagonist that known to impair learning ability and memory function. Scopolamine can block central cholinergic neuronal activity that is associated with neurogenesis and cell proliferation in the hippocampus. So it is used to induce an AD model in animal (Heo et al. 2014a, b). Scopolamine increased MDA while decreased SOD, thiol concentrations and NO level in hippocampus (Azizi-Malekabadi et al. 2012; Hosseini et al. 2015; Karimi et al. 2015; Mohammadpour et al. 2015). Also AChE activity in the cortical tissues was higher in the scopolamine group than the control group (Hosseini et al. 2015). The latency and path length in MWM test and the latency to enter the dark compartment in PA test in the scopolamine group were higher than control (Azizi-Malekabadi et al. 2012; Hosseini et al. 2015; Jamialahmadi et al. 2013; Karimi et al. 2015; Mohammadpour et al. 2015).

The beneficial effect of exercise in this animal model of AD is shown to be mediated via inhibition of AChE expression and activation of BDNF-TrkB pathway. Treadmill exercise (5 m/min, 30 min, for 2 weeks) alleviates short-term memory impairment that was evaluated in the step-down avoidance task induced by i.p. injection of scopolamine hydrobromide (1mg/kg) in mice. Animal training inhibited AChE expression (immediately after determining the latency in the step-down test), so had a therapeutic role for scopolamine-induced amnesia in mice (Heo et al. 2014b). Other beneficial effects of exercise in similar animal model have also been demonstrated. Treadmill exercise increased spatial learning ability in MWM test and activated BDNF-TrkB pathway and elevated cell proliferation in hippocampus, therefore, prevented spatial learning deficit in amnesia mice (immediately after determining occupancy time) (Heo et al. 2014a).

Streptozotocin-induced Alzheimer

Diabetes mellitus is associated with a high risk of cognitive impairments such as explicit memory and attention. Intraperitoneal injection of streptozotocin (STZ) is an accepted rodent model of diabetes, which induces Aβ deposition, impairment of neural plasticity, synapse loss, hippocampal atrophy. Those effects have been related to oxidative stress, metabolic disturbance and neuroinflammation which have been induced by STZ injection (Wang et al. 2014). It has been demonstrated that MDA concentration was increased while SOD activity and glutathione (GSH) concentration was decreased in the brain of diabetic rats (Mao et al. 2015; Mousavi et al. 2015). Imbalance in ROS concentration and natural antioxidant system may cause neuronal apoptosis. These changes may lead to memory and learning deficit and cognitive decline (Mao et al. 2015; Wang et al. 2014). STZ injection impaired spatial learning and memory as in MWM test the latency time and path length were higher, in the diabetic animals than control (Ghasemi et al. 2016; Mousavi et al. 2015). Exercise with different intensity (8-16 m/min) and duration (30-60 min; 2-12 weeks) may alleviate diabetes induced memory and learning impairment. It has been indicated that long-term treadmill exercise (V=16.6 m/min, 30 min/day for 6 weeks) attenuates impairment of neuroplasticity and associated with memory decline in the STZ-induced (50 mg/kg, i.p.) AD in rats. This study suggests that moderate exercise caused better performance in radial arm maze task (once a week over a 6-week period) and enhanced neuronal immediate-early gene expression associated with neuroplasticity (immediately) in dentate gyrus of hippocampus, so recovery of spatial memory (You et al. 2009). Treadmill exercise (V=8 m/min, 30 min/day for 12 weeks) also improves short-term memory deficits in the step-down avoidance task (on the last day of treadmill exercise) and disability of spatial learning in the 8-arm radial maze test induced by i.p. injection of STZ (50 mg/kg) in diabetic rats. Diabetes decreased 5-bro-mo-2'-deoxyridine (BrdU)-positive and doublecortin (DCX)-positive cells in the hippocampal dentate gyrus, while exercise increased them. In addition, STZ decreased Wnt3 pathway that acts as a controller of synaptic plasticity, long-term potentiation (LTP) and glycogen synthase kinase-3β (GSK-3β) expression. The finding of this study also suggests that exercise enhanced Wnt3 expression and inhibited GSK-3β expression, so improve short-term memory impairment and spatial learning disability (Kim et al. 2016). Treadmill exercise (V=8.2 m/min, 60 min/day for 5 weeks) reduced glial fibrillary acidic protein (GFAP) while, increased S100B level of cerebrospinal fluid and hippocampus (in the day after the behavioral analysis) and prevented spatial memory deficits through better performance novel object-placement recognition (NOPR) task (One day after the last training session) in diabetic rat. Therefore, exercise prevents astroglial alterations cognitive impairments in diabetes induced by intravenous (i.v.) injection of STZ (50 mg/kg) into the tail vein (de Senna et al. 2011).

It has been indicated that aerobic exercise (V=15 m/min, 60 min/day for 5 weeks) improves spatial memory deficit of i.v.

injection of STZ (50 mg/kg) that was evaluated by place recognition (PR) test before and after exercise protocol. Behavioral results reported that exercise reverted the reduction of spent time exploring the relocated object in non-trained diabetic rats and the animal of trained diabetic spent more time exploring the relocated object than non-trained diabetic group. Also result showed that exercise increases the astrocytic ramification and the density of GFAP positive astrocytes (one day after last PR test) in diabetic animals, so reduced impairment of spatial memory in diabetic rats (de Senna et al. 2017).

Moreover, it had been shown that postnatal treadmill exercise (V=8 m/min, 30 min/day for 2 weeks) improves short-term memory impairment of STZ injection (40 mg/kg, i.p.) in rat pups born to diabetic rats. This study suggests that postnatal treadmill exercise increased The latency of the step-down avoidance task and the cell proliferation and suppressed apoptosis in the hippocampal dentate gyrus (Immediately after determination of the retention time) and may be used for treatment of neurodevelopment deficits in children born to diabetic mothers (Kim et al. 2014).

The intracerebroventricular (ICV) injection of STZ induces impairment in brain glucose and energy metabolism by desensitization of insulin receptors and increase oxidative stress damage to neural cells. It changed synaptic protein level and insulin/IGF-1 signaling, as well as increased hyperphosphorylated tau in the brain (Chen et al. 2013). In addition, the single ICV injection could induce chronic neuroinflammation, atrophy and neural cell loss in septum region of the brain as well as ventricles dilation (Kraska et al. 2012). So the ICV injection of STZ has been used in animal models of AD (de Senna et al. 2017; Jee et al. 2008; Muller et al. 2012; Shima et al. 2017).

Exercise ameliorates neurodegenerative effects of ICV injection of STZ as another rat model of AD. Treadmill exercise (V=8 m/min, 30 min/day for 2 weeks) improves long-term memory deficits through reversed the STZ-induced decrease the latency time in step-through passive avoidance task and increased c-Fos expression (immediately after the completion of the final exercise) in the rats after ICV injection of STZ (1.5 mg/kg) (Jee et al. 2008). In addition, treadmill exercise (V=8 m/min, 30 min/day for 4 weeks) can improve the behavioral task such as enhance the correct choice and decline the number of error and completed time in 8-arm radial maze test, as well as increased cell proliferation and BDNF and tropomyosin receptor kinase B (TrkB) expressions (immediately after behavioral test) in hippocampus of diabetic rats (ICV injection of STZ, 1.5 mg/kg) (Sim 2014).

Otsuka Long–Evans Tokushima Fatty rat is a model of human type 2 diabetes and animal exhibits memory dysfunction and hyperglycaemia. Shima et al. study showed that moderate treadmill exercise (V=25 m/min, 30min/day for 4 weeks) improves memory dysfunction in this model. Moderate exercise improved hippocampal function in MWM test and enhanced glycogen levels and normalized the monocarboxylate transporter 2 (MCT2) expression in the hippocampus, therefore ameliorate spatial memory deficits induced by type 2 diabetes (Shima et al. 2017). However, exercise may worsen the insulin resistance which has been induced by STZ (1-3 mg/kg) ICV injection. In a study ICV administration of STZ before treadmill running (V=free for 4 weeks) aggravate memory deficits and regulation of mitochondrial H_2O_2 while treadmill exercise lead to better performance in MWM test. The authors concluded that blockage of insulin signalling could reduce the beneficial effects of exercise on memory performance (Muller et al. 2012).

The results of the above mentioned studies showed that treadmill exercise may improve diabetes induce neurodegenerative disorders and memory deficits by following mechanisms. It increased neuronal immediate-early gene c-Fos expression associated with neuroplasticity, blood brain barrier (BBB) integrity, cell proliferation and BDNF, TrkB and Wnt3 expressions, release of neurotrophic factors, hippocampal neural plasticity, LTP, astrocytic proliferation and neurogenesis in hippocampus. Exercise normalized of MCT2 expression in the hippocampus, suppressed apoptosis in the hippocampal dentate gyrus and inhibited hippocampal GSK-3β expression.

Table 2 summarizes the neuroprotective effects of exercise in neurotoxin-induced Alzheimer models.

Effect of exercise on hormonal and other disorders inducing memory deficiency

Cerebral ischemia induced memory deficiency

Cerebral ischemia is induced by decrease cerebral blood flow and permanent occlusion of cerebral arteries. Transient ischemic attacks can cause neurological deterioration of the hippocampus that lead to deficit of memory and other cognitive functions (Ahn et al. 2016; Shih et al. 2013; Sim et al. 2004).

It had been shown that treadmill exercise (V=8 m/min, 30 min/day for 10 days) ameliorates short-term memory impairment ischemic gerbils. Treadmill running increased granular cell proliferation and neurogenesis in the dentate gyrus and suppressed apoptotic neuronal cell death, so improved ischemia-induced cognition deficit and memory impairment (Sim et al. 2004). Shih et al. study showed that mild and moderate treadmill exercise (V mild=8 m/min, V moderate=25 m/min, 30 min/day for 14 days) affects the spatial memory performance that was evaluated by MWM test in the brain ischemic rats. These results showed that mild exercise increased the levels of BDNF and postsynaptic density protein 95 (PSD-95), but not in moderate exercise, thus low intensity exercise could improve impairment of spatial memory and synaptic plasticity better than high intensity exercise

Table 2 Effects of exercise in neurotoxin-induced memory deficiency

Experimental model	Exercise protocol	Molecular and structural effect	Behavioral test and effect	Reference
Amyloid β male rat	V=15 m/min, 60 min/day for 4 weeks	↑BDNF and p-CaMKII levels, activation of E-LTP and ↓up regulation of calcineurin	↑short-term memory (RAWM test)	(Dao et al. 2013)
Amyloid β male rat (7 weeks)	V=8 m/min, 30 min/day for 4 weeks	↑neurogenesis and expressions of BDNF and trkB	↑short-term memory (step-through avoidance test)	(Kim et al. 2015b)
Ethanol Prenatal male rat	voluntary exercise for five consecutive days	↑LTP induction and BDNF levels	↑spatial learning and memory (MWM test)	(Christie et al. 2005)
Ethanol adult male rat	V=17 m/min, 60 min/day for 4 week	↓ethanol induced memory deficiency	↑spatial learning and memory (MWM test)	(Hashemi Nosrat Abadi et al. 2013)
LPS male mice (8 weeks)	V=10 m/min, 60 min/day for 5 weeks	↑BDNF and TrkB expression	↑spatial learning and memory (MWM test)	(Wu et al. 2007)
LPS male rat (6 weeks)	V=10 m/min, 30 min/day for 6 weeks	↓DCX expression and ↑NeuN expression and neuronal maturation	↑short-term memory (step-down avoidance test)	(Kim et al. 2013)
LPS rat pup	V=8-14 m/min, 30 min/day for 4 weeks	↑BDNF and TrkB expression and cell proliferation and neurogenesis	↑short-term memory (step-down avoidance test)	(Kim et al. 2015a)
LPS neonatal rat	V=8 m/min, 30 min/day for 4 weeks	Activates PI3K-AKT pathway and ↑synaptic plasticity and neurogenesis	↑short-term memory (step-down avoidance test)	(Jung and Kim 2017)
Morphine male rat (6 weeks)	V=10 m/min, 60 min/day for 10 weeks	-	↑spatial learning and memory (MWM test)	(Zarrinkalam et al. 2016)
Morphine adult female rat	V=10 m/min for mild and 22 m/min for severe, 30 min/day for 4 weeks	-	mild: ↓anxiety levels (EPM test) ; severe: ↑spatial memory (OLMT)	(Ghodrati-Jaldbakhan et al. 2017)
Scopolamine male mice	V=5 m/min, 30 min, for 2 weeks	↓AChE expression	↑short-term memory (step-down avoidance test)	(Heo et al. 2014b)
Scopolamine male mice	V=5 m/min, 30 min, for 2 weeks	activated BDNF-TrkB pathway and ↑ cell proliferation	↑spatial learning (MWM test)	(Heo et al. 2014a)
STZ male rat (12 weeks)	V=16.6 m/min, 30 min/day for 6 weeks	↑neuronal immediate-early gene expression associated with neuroplasticity	↑spatial memory (radial arm maze test)	(You et al. 2009)
STZ male rat (7 weeks)	V=8 m/min, 30 min/day for 12 weeks	↑BrdU-positive and DCX-positive cells and ↓GSK-3β expression	↑short-term memory (step-down avoidance test) and spatial learning (8-arm radial maze test)	(Kim et al. 2016)
STZ male rat (3 months)	V=8.2 m/min, 60 min/day for 5 weeks	↓GFAP, ↑S100B level of cerebrospinal fluid and hippocampus	↑spatial memory (NOPR test)	(de Senna et al. 2011)
STZ male rat (3 months)	V=15 m/min, 60 min/day for 5 weeks	↑astrocytic ramification and density of GFAP positive astrocytes	↑spatial memory (PR test)	(de Senna et al. 2017)
STZ rat pup	V=8 m/min, 30 min/day for 2 weeks	↑the cell proliferation and ↓apoptosis	↑short-term memory (step-down avoidance test)	(Kim et al. 2014)
STZ male rat (9 weeks)	V=8 m/min, 30 min/day for 2 weeks	↑c-Fos expression	↑long-term memory (step-through passive avoidance test)	(Jee et al. 2008)
STZ male rat (40 weeks)	V=8 m/min, 30 min/day for 4 weeks	↑cell proliferation and BDNF and TrkB expressions	↑spatial learning (8-arm radial maze test)	(Sim 2014)
STZ male rat (4 weeks)	V=25 m/min, 30 min/day for 4 weeks	↑glycogen levels and normalized of MCT2 expression	↑spatial memory (MWM test)	(Shima et al. 2017)
STZ male mice (2 months)	V=free for 4 weeks	Improve Insulin Regulation of H_2O_2 Production	↑spatial memory (MWM test)	(Muller et al. 2012)

BDNF, brain-derived neurotrophic factor; *p-CaMKII*, phosphorylated calcium calmodulin dependent protein kinase II; *LTP*, long-term potentiation; *RAWM*, radial arm water maze; *TrkB*, tropomyosin receptor kinase B; *MWM*, Morris water maze; *DCX*, doublecortin; *NeuN*, neuronal nuclear antigen; *PI3K*, phosphatidyl inositol 3-kinase; *AKT*, serine/threonine protein kinase; *EPM*, elevated plus maze; *OLMT*, object location memory task; *AChE*, acetylcholinesterase; *BrdU*, 5-bro-mo-2'-deoxyridine; *GSK-3β*, glycogen synthase kinase-3β; *GFAP*, glial fibrillary acidic protein; *NOPR*, novel object-placement recognition; *PR*, place recognition; *MCT2*, monocarboxylate transporter 2

(Shih et al. 2013). Moreover, it had been indicated that treadmill exercise (V=12 m/min, 30 min/day for 12 weeks) ameliorates spatial learning impairment in pups with brain injury which had been induced by hypoxic ischemia. The results suggest that treadmill running increased the time spent in the probe quadrant in MWM test and expression of dopamine and ameliorated loss of dopaminergic fibers in the striatum (after the completion of last treadmill exercise), so improved spatial learning ability (Park et al. 2013). Other intensity of treadmill exercise (V=10 m/min, 30 min/day for 4 weeks) also alleviates memory deficits in ischemic gerbils. Long-term treadmill exercise improved short-term memory function after ischemic stroke through increased the latency in passive avoidance test and restoration of myelin and increased cell proliferation and neuronal maturation and BDNF levels (Ahn et al. 2016).

Treadmill exercise (V=15 m/min, 30 min /day for 1 weeks) improves memory dysfunction in MWM test after cerebral embolism that induced by intra-arterial microsphere. In this study exercise was started at 24 hours (early group) or 8 days (late group) after injection. The BDNF levels in both groups have been increased which resulted in cognitive function improvement (Himi et al. 2016). Moreover, low intensity treadmill exercise (V=8 m/min, 30 min/day for 4 weeks) improves impairment of memory function in object recognition test (ORT), object location test (OLT) and passive avoidance test (PAT) after cerebral infarction in rats. Exercise increased neurogenesis in the hippocampal dentate gyrus and decreased infarct volumes, so has positive effects on memory deficits in stroke rats (Shimada et al. 2013).

Hypothyroidism induced memory deficiency

Thyroid hormones are necessary for normal brain development and function. These hormones increase neurogenesis in the hippocampus, so thyroid hormone insufficiency causes disorders of memory and spatial learning ability (Beheshti et al. 2017; Park and Song 2016; Shafiee et al. 2016). Previous studies showed that hypothyroidism increased the escape latency and traveled path in MWM and decreased delay in entering the dark compartment in PA test (Baghcheghi et al. 2017, 2018). Increase in MDA and NO metabolites and reduction in the thiol content and SOD and CAT activities have been introduced as one of the probable mechanism of hypothyroidism induced memory deficiency (Baghcheghi et al. 2017, 2018).

Shafiee et al. study indicated that voluntary and treadmill exercise (V=8 m/min, 30 min/day for 2 weeks) can improve deficit of learning and memory in hypothyroid rat pups. This study shows that short-term treadmill exercise and the voluntary wheel exercise can improve behavioral function in water maze and alleviate neurochemical deficits and cognitive impairment through increase BDNF level in hippocampus (Shafiee et al. 2016). In addition, treadmill exercise (V=25 m/min, 30 min/day for 4 weeks) ameliorates the impairment of spatial learning caused by hypothyroidism in adult rats. The findings of this study suggest that both aerobic and anaerobic exercises returned the levels of thyroid hormone to normal levels and alleviated lethargy in open field (OF) test and spatial learning disability in MWM test, but the animals of anaerobic exercise group had more movement in open field and greater time reductions in MWM test than aerobic exercise group. So, for improving symptoms of learning impairment, anaerobic exercise is more valuable than aerobic exercise (Park and Song 2016).

Multiple sclerosis induced memory deficiency

Multiple sclerosis (MS) is the autoimmune diseases which is common in young adults. It can decrease the myelination of oligodendrocytes and axons in the CNS. The axonal demyelination blocks axonal transmission that induced functional impairments, including cognitive deficits (Jin et al. 2014; Kim and Sung 2017).

Kim et al. reported that regular treadmill exercise (V=5 m/min, 30 min/day for 4 weeks) ameliorates long-term memory deficits induced by MS after experimental autoimmune encephalomyelitis (EAE) in mice. The results suggest that treadmill exercise increased the latency in the step-down avoidance task and suppressed demyelination and apoptosis and increased cell proliferation and BDNF expression (immediately after behavioral test) in hippocampal dentate gyrus, thus improved memory deficits in EAE mice (Kim and Sung 2017).

Ovariectomy induced memory deficiency

Estrogen has an important role in modulating the physiological functions of the brain. It can increase synaptogenesis and regulate expressions of neurotrophins such as IGF or BDNF. It has been demonstrated that the decrease of estrogen levels by ovariectomy caused dysfunctions of the hippocampus (Hosseini et al. 2011; Kaidah et al. 2016). It has been shown that ovariectomy increased MDA and decreased thiol concentration in the hippocampus (Zabihi et al. 2014). Behavioral test was also impaired in ovariectomized (OVX) animals. It has been demonstrated that time latency and path length in MWM were higher and the animals time spent in the target quadrant (Q1) during the probe trial was lower in the OVX group than the control (Azizi-Malekabadi et al. 2011; Hosseini et al. 2010, 2011; Zabihi et al. 2014).

It was indicated that treadmill exercise (V=18 m/min, 60 min/day for 12 weeks) improved impairment of spatial memory in ovariectomized rats. In this study regular treadmill exercise leads to better performance in memory persistence test and enhanced estrogen levels (24 h after the last exercise training) in the hippocampus and improved ovariectomy-induced impairment of spatial memory of Sprague Dawley rats (Kaidah et al. 2016). Cui et al. study showed that treadmill exercise (V=for 8 weeks) alleviates spatial learning and memory impairment induced by ovariectomy in rats. These findings suggest that regular treadmill exercise increased the performance in 8-arms radial maze test and suppressed oxidative stress and up-regulate nNOS expression in marginal division of the striatum (Cui et al. 2018).

Sleep deprivation induced memory deficiency

Sleep plays an essential role in normal physiological functions of the body and has the positive effects on procedural and consolidation of memory. Sleep disorders (SD) induce impairment of hippocampal dependent learning and memory (Fernandes et al. 2013; Saadati et al. 2015; Salari et al. 2015).

It has been indicated that treadmill exercise (V=15 m/min 5 days a week for 4 weeks with incremental session (2-4)) improves long-term memory impairment in RAWM test following 24 hours SD in amnesia rats. The results suggest that treadmill exercise improved the RAWM performance and increased in the basal levels of calcium/calmodulin kinase IV (CaMKIV), MAPK/ERK, and BDNF in the cornu ammonis 1 (CA1) area of the hippocampus, so ameliorated long-term memory decline and synaptic plasticity (Zagaar et al. 2013). Moreover, Fernandes et al. reported that treadmill aerobic exercise (V=18 m/min, 25 min/day for 4 weeks) reduces 96 hours of paradoxical sleep deprivation (PSD)-induced memory impairment in rats. These results have shown that aerobic exercise could reduce the cognitive effects of SD on long-term memory and had a neuroprotective role in this study (Fernandes et al. 2013).

Short-term treadmill exercise (V=15 m/min, 60 min/day for 4 days) also ameliorates cognitive impairments induced by 72 hours PSD in the female rats. Treadmill exercise improved performance in MWM test (30 min after the PSD paradigm) and had an effective role against impairments induced by PSD on learning and memory ability (Saadati et al. 2015).

In another study similar regime of treadmill exercise improves impairment of long-term memory after induction of 4 hours SD in female rats. Regular treadmill exercise increased time spent in target quadrant of MWM test (30 min after the end of the SD period) and had neuroprotective and beneficial effects on synaptic and molecular changes cause by SD and alleviated long-term memory deficit in rats (Salari et al. 2015).

Stress induced memory deficiency

Stress causes many changes to the neural responses of the brain and can induce dendritic spine loss in hippocampus and affects neural plasticity to cause deficits in memory and learning ability (Chen et al. 2017; Kim and Leem 2016).

It has been shown that regular treadmill exercise (19 m/min, 60 min/day, 3 weeks) reverses memory deficits induced by chronic stress (6 hours /day for 21 days). In this model of memory deficit, regular and prolonged treadmill exercise improves chronic stress-induced memory impairment through improved the reduction of alternation in the Y-maze and increased memory retention in the water maze test, as well as increased adenosine monophosphate activated protein kinase (AMPK)-mediated BDNF induction and increasing neurogenesis in the hippocampus (Kim and Leem 2016). Chen et al. study showed that treadmill exercise (12 m/min, 60 min/day) improves working memory impairment induced by stress (restrained for 1 hour daily for 14 consecutive days). This study demonstrated that treadmill running ameliorates stress related behavioral impairments in open field test and elevated plus maze (EPM) test, as well as improved working memory deficit induced by stress via increasing BDNF and TrkB expression and facilitating spine retention (Chen et al. 2017). In addition, treadmill exercise (incremental speed 5 m/min every 3 min until exhaustion, 50 min/day for 8 weeks) could alleviates short- and long-term recognition memory deficits in object recognition test and short- and long-term aversive deficits in inhibitory avoidance test in the maternal deprived rat pups. In this study, exercise (VO2 =50-70% max) prevents oxidative in the hippocampus and prefrontal cortex (Neves et al. 2015). It was reported that treadmill running (9-15 m/min, 10-60 min/day for 6 weeks) alleviated spatial memory deficits induced by post-traumatic stress disorder (PTSD) in adult male rats. In this model, regular exercise enhanced the central corticotropin releasing factor receptor 1 (CRFR1) expression in hypothalamus, amygdala and the prefrontal cortex and regulated the hypothalamic–pituitary–adrenal (HPA) axis function. Also, long-term regular treadmill exercise improved stress-induced behavior in the open field test and elevated plus maze (EPM) test and alleviated spatial memory impairment through increase the ratio of entry to the novel arm and ratio of time spent in the novel arm in the Y maze test (Li et al. 2015).

Transgenic mouse models for memory deficiency

Transgenic mice are other common models for AD. These models help to expand our knowledge about molecular mechanisms of AD and new healing strategies. Inducing mutation in amyloid precursor protein (APP), presenilin-1 (PS1) and presenilin-2 (PS2) genes are commonly used transgenic mouse models for research (Kitazawa et al. 2012). In these models early overproduction and deposition of Aβ would cause memory deficiency, neuroinflammation and neurodegeneration (Nazem et al. 2015). Although these models could not mimic the human process of AD disease, however neuropathological marker, including synaptic loss, LTP and neurochemical signals deficit, activated microglia and increased innate immune and inflammatory responses have been demonstrated in these models (Kitazawa et al. 2012). Long-term treadmill exercise (V=11-15 m/min, 20-30 min/day for 5 months) ameliorates cognitive impairments of AD in APP/PS1 mouse model. Exercise decreased the escape latency in MWM (After 5-month exercise) and decreased activated microglia and elevated BDNF-positive cells in cerebral cortex and the hippocampus, increased LTP and BDNF mRNA expression in hippocampus but did not decrease the accumulation of β-amyloid (Liu et al. 2011; Xiong et al. 2015). Lin et all reported that treadmill exercise (V=10-12 m/min, 20-60 min/day for 9 weeks) lead to better performance in Pavlovian fear conditioning tasks that evaluated hippocampus and amygdala associated memories, also increased the hippocampus-associated long-term memory through enhance of neuronal function in CA1 and CA3 and improve amygdala-associated long-term memory via increase of BDNF signaling pathways, neuronal function and β-amyloid clearance in APP/PS1 transgenic mice (Lin et al. 2015). Amygdala and hippocampus are two most important structures of temporal lobes that neurodegeneration in these regions are as indicator for quick onset of AD (Jack and Holtzman 2013). So, physical exercise can prevent from cognitive impairment and delay the onset of AD in transgenic mice by the enhancement of hippocampus- and amygdala-associated neuronal function (Lin et al. 2015)

Table 3 summarizes the neuroprotective effects of exercise on hormonal and other disorders induced memory deficiency.

Discussion

Although several human studies revealed the beneficial effects of exercise on learning, memory and cognition, however, regarding to limitation and confonders in such studies, different rodent models of AD has been designed. In these animal models the protective effects of exercise on Alzheimer's induced neurodegenerative and neuroinflammatory process have been demonstrated. The common protective mechanisms of exercise in different models are increasing the hippocampal neurogenesis and plasticity; suppressing apoptosis in the hippocampal dentate gyrus and balancing the oxidant-antioxidant system. The results of more than ninety animal studies showed that neuromodulatory effects of exercise including; increase in immediate-early gene c-Fos expression in dentate gyrus; enhancing the Wnt3 expression and inhibiting GSK-3β expression; increasing the BrdU-positive and DCX-positive cells; increasing in level of astrocytes GFAP and decreasing in S100B protein, increase in BBB integrity; prevention of oxidative stress injury, inducing morphological changes in astrocytes of the stratum radiatum of CA1 area; increase in cell proliferation and suppress in apoptosis in dentate gyrus; increase in BDNF and TrkB expressions; enhancing the glycogen levels and normalizing the MCT2 expression. To the best of our knowledge, there is no rodent animal study investigated the maintenance of exercise beneficial effects on cognition during the recovery period (more than one week) after training. However the impact of exercise on molecular pathways which enhance the short and long term memory as well as brain structural changes, including increasing in volume, surface area and total length of cortical capillary, neurogenesis, neural plasticity and restoration of presynaptic density in hippocampus (as main region associating in spatial memory and the consolidation of declarative memory) have been demonstrated (Wang et al. 2015). These effects imply the concept of long lasting effect of exercise on memory related brain structures. In addition, most of the experiments investigated the molecular and super molecular memory and cognitive enhancing effect of exercises on hippocampus and to a lesser extent on striatum, amygdala, prefrontal cortex and cortex (the specific region not mentioned). Moreover the modulatory effects of exercise on hypothalamus, basal ganglia and brain stem regions have been demonstrated. These regions may be related to cognitive process by affecting the basic CNS function including; regulation of circadian rhythm, the body metabolism and the response to stress (Morgan et al. 2015). The positive effect of exercise on cerebellum damage (reactive astroyctes formation and Purkinje cell loss) after brain injury have been shown (Seo et al. 2010) which may be effective in motor learning and memory. The impact of exercise on other brain regions which contributed to cognitive process, including other part of the limbic system, different lobe of cortex, and cerebellum should be deeply investigated in future studies. Most of the above mentioned rodent studies showed the beneficial effect of long term treadmill exercise on behavioral tests and molecular mechanism related to long term memory (spatial, object recognition and passive avoidance test after 24h) and there are few studies mentioned the effects on working and short term memory or other types of memory. Most of these mild to moderate training protocols (long-term) had been done on male rats with the speed of 5-25 m/min and the duration of 4 days-14 month. There was one short bout exercise protocol (duration of 4-6 min) with no effect on short term memory.

In conclusion, although there are ample evidence of molecular and spuramolecular beneficial effects of exercise on memory, the effects of exercise on different phases of memory formation (encoding and consolidation) had not been evaluated. In addition, most of rodent models exploring the effect of exercise on Alzheimer used long term protocols, and evaluated the hippocampal related molecular mechanisms and tasks. Moreover, there are some controversies between the results of these studies (effective in long term memory) and human studies (small effect on long term memory). Therefore, more experiments using both sexes of animals should be designated to investigate the effects of different types of exercise (acute and chronic) on different types of memory and related brain structure in future.

Table 3 Effect of exercise on hormonal and other disorders inducing memory deficiency

Experimental model	Exercise protocol	Molecular and structural effect	Behavioral test and effect	Reference
Cerebral ischemia male gerbil (11–13 weeks)	V=8 m/min, 30 min/day for 10 days	↑granular cell proliferation and neurogenesis and ↓apoptotic neuronal cell death	↑short-term memory	(Sim et al. 2004)
Cerebral ischemia male rat (8 week)	V=8 m/min, 30 min/day for 14 days	↑the levels of BDNF and PSD-95	↑spatial memory (MWM test)	(Shih et al. 2013)
Cerebral ischemia rat pup	V=12 m/min, 30 min/day for 12 weeks	↑expression of dopamine and ameliorated loss of dopaminergic fibers in the striatum	↑spatial learning (MWM test)	(Park et al. 2013)
Cerebral ischemia male gerbil (22-24 months)	V=10 m/min, 30 min/day for 4 weeks	↑myelin and ↑cell proliferation and neuronal maturation and BDNF levels	↑short-term memory (passive avoidance test)	(Ahn et al. 2016)
Cerebral ischemia male rat (9 weeks)	V=15 m/min, 30 min/day for 1 weeks	↑BDNF levels	↑spatial memory (MWM test)	(Himi et al. 2016)
Cerebral ischemia male rat (7 weeks)	V=8 m/min, 30 min/day for 4 weeks	↑neurogenesis gyrus and ↓infarct volumes	↑recognition memory (ORT) and spatial memory (OLT)	(Shimada et al. 2013)
Hypothyroidism rat pup	V=8 m/min, 30 min/day for 2 weeks	↑BDNF level	↑behavioural function (WM)	(Shafiee et al. 2016)
Hypothyroidism male rat	V=25 m/min, 30 min/day for 4 weeks	return the levels of thyroid hormone to normal levels and ↓symptoms of learning impairment	↓lethargy (OF test) and ↑spatial learning (MWM test)	(Park and Song 2016)
MS female mice (10 weeks)	V=5 m/min, 30 min/day for 4 weeks	↓demyelination and apoptosis and ↑cell proliferation and BDNF expression	↑long-term memory (step-down avoidance test)	(Kim and Sung 2017)
Ovariectomy female rat (12 weeks)	V=18 m/min, 60 min/day for 12 weeks	↑estrogen levels in hippocampus	↑spatial memory (memory persistence test)	(Kaidah et al. 2016)
Ovariectomy female rat	for 8 weeks	↓oxidative stress and up-regulate nNOS expression in MrD	↑spatial learning and memory (8-arms radial maze test)	(Cui et al. 2017)
Sleep deprivation male rat (45-48 days)	V=15 m/min for 4 weeks	↑the basal levels of CaMKIV, MAPK/ERK, and BDNF in CA1	↑long-term memory (RAWM test)	(Zagaar et al. 2013)
Sleep deprivation	V=18 m/min, 25 min/day for 4 weeks	-	↑long-term memory	(Fernandes et al. 2013)
Sleep deprivation female rat (3–4 months)	V=15 m/min, 60 min/day for 4 days	-	↑spatial learning and memory (MWM test)	(Saadati et al. 2015)
Sleep deprivation female rat	V=15 m/min, 60 min/day for 4 days	neuroprotective and beneficial effects on synaptic and molecular changes cause by Sleep deprivation	↑spatial long-term memory (MWM test)	(Salari et al. 2015)
Stress male mice (7 weeks)	V=19 m/min, 60 min/day, 3 weeks	↑AMPK-mediated BDNF and ↑neurogenesis	↑memory function (Y-maze tests)	(Kim and Leem 2016)
Stress male mice	V=12 m/min, 60 min/day	↑BDNF and TrkB expression and facilitating spine retention	↓stress related behavioral impairments (OF test and EPM) and ↑ working memory	(Chen et al. 2017)
Stress male rat pup (21 days)	Incremental speed 5m/min every 3 min until exhaustion, 50 min/day for 8 weeks	↓oxidative in hippocampus and prefrontal cortex	↑short- and long-term recognition memory (object recognition test) and short- and long-term aversive memory (Inhibitory avoidance test)	(Neves et al. 2015)
Stress adult male rats	V= 9-15 m/min, 10-60 min/day, 6 week	↑CRFR1 expression, regulation HPA axis function	stress related behavioral impairments (OF test and EPM) and ↑spatial memory (Y maze test)	(Li et al. 2015)
Transgenic male mice	V=11-15 m/min, 20-30 min/day, 5 months	↑BDNF-positive cells, ↓activation of microglia	↑spatial memory (MWM test)	(Xiong et al. 2015)
Transgenic mice	V=11-15 m/min, 30 min/day, 5 months	↑BDNF mRNA expression and LTP	↑spatial learning and memory (MWM test)	(Liu et al. 2011)
Transgenic mice (4 months)	V=10-12 m/min, 20-60 min/day, 9 weeks	↑BDNF signaling pathways, neuronal function, β-amyloid clearance	↑long-term memory (Pavlovian fear conditioning tasks)	(Lin et al. 2015)

MWM, Morris water maze; *BDNF*, brain-derived neurotrophic factor; *PSD-95*, postsynaptic density protein 95; *ORT*, object recognition test; *OLT*, object location test; *WM*, water maze; *OF*, open field; *nNOS*, Neuronal nitric oxide synthase; *MrD*, marginal division of the striatum; *CaMKIV*, calcium/calmodulin kinase IV; *MAPK*, mitogen-activated protein kinase; *ERK*, extracellular signal-regulated protein kinase; *RAWM*, radial arm water maze; *AMPK*, adenosine monophosphate activated protein kinase; *TrkB*, tropomyosin receptor kinase B; *EPM*, elevated plus maze; *CRFR1*, central corticotropin releasing factor receptor-1; *HPA*, hypothalamic–pituitary–adrenal; *LTP*, long-term potentiation

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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