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Can exercise ameliorate aromatase inhibitor-induced cognitive decline in breast cancer patients?

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Abstract

Aromatase inhibitors (AIs) have been commonly used as an effective adjuvant therapy in treatment of breast cancer, especially for menopausal women with estrogen receptor positive breast cancer. Due to the nature of aromatase, the key enzyme for endogenous estrogen synthesis, inhibitory of aromatase-induced side effects, such as cognitive impairment has been reported in both human and animal studies. While extensive evidences suggested that physical exercises can improve learning and memory activity and even prevent age-related cognitive decline, basic research revealed some common pathways between exercise and estrogen signaling that affected cognitive function. This review draws on clinical and basic studies to assess the potential impact of exercise in cognitive function from women treated with AIs for breast cancer and explore the potential mechanism and effects of exercise on estrogen-related cognition.

Keywords

breast cancer; aromatase inhibitors; exercise; cognition

Introduction

Aromatase is a key enzyme in estrogen synthesis and is widely expressed in many tissues, such as ovary, breasts and brain. Unlike ovary-synthesized estrogen, which is mainly released into the bloodstream, brain-synthesized estrogen mostly acts locally to maintain brain functions under normal conditions and plays neuroprotective roles in age-related cognitive decline and even Alzheimer's disease (AD) [1,2]. Brain aromatase is important for maintaining local endogenous estrogen levels. Studies showed that reduction of brain aromatase is directly linked to decline of cognitive function and risk of AD in females [2–7].

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Breast cancer is one of the top cancers that occur frequently in women and about 75% of all breast cancers are estrogen receptor-positive [8]. Estrogen receptor-positive breast cancer is directly associated with over-proliferation of mammary gland epithelial cell by the stimulation of estrogen. Therefore, inhibition of estrogen synthesis and reduction of estrogen level has been an effective treatment to decrease the incidence of estrogen receptor-positive breast cancer. During the past decade, aromatase inhibitors (AIs) have been widely used as a standard therapy for estrogen receptor-positive breast cancer, which accounts for majority of the invasive breast tumors in postmenopausal woman [8]. Clinically, AIs are generally well tolerated; however, increasing basic and clinical reports suggest that AIs therapy may be associated with long-term cognitive impairment in some breast cancer patients, especially in breast cancer survivors [9–11]. Other side effects of AIs are also reported which include osteoporosis, and bone fracture [12,13]. Increasing evidence showed that exercise can boost patients' immunity, reduce inflammation, and relieve joint pain during treatment of breast cancers [14,15]. It is also well recognized that exercise can improve cognitive function and prevent age- and disease-related cognitive decline including estrogen deficiency-induced cognitive impairment [16]. However, it is unknown that whether exercise could prevent the risk of cognitive decline induced by AIs treatment. In this review, we will focus on the potential exercise intervention in cognitive decline caused by AIs treatment.

Protection of estrogen on cognitive

Estrogen not only plays an important role in reproduction but also modulate cognition process, especially learning and memory. Recently, a cognitive function study recruited 1884 women with 8 years annual following up and found that subjects with surgical menopause at early age had faster decline in global cognition, specifically episodic memory and semantic memory compared to age-matched women underwent natural menopause [17]. It is also suggested that women of surgical menopause were more likely engaged in cognitive impairment that primarily affected verbal episodic memory in later life compared with women of natural menopause [18]. In addition, the same study also reported that earlier onset of menopause was associated with increased AD neuropathology, especially neuritic plaques which had been proved that resulted from estrogen deficiency [17]. Furthermore, while some studies demonstrated controversial findings of a correlation between plasma estrogen levels and cognitive function in elderly women, more recent investigations found that the level of brain estrogen is directly associated with risk of AD in aged females [5–7]. Early and long-term hormone replacement therapy was associated with reduction of the age-related global cognition decline [17]. And these results were consistent with previous studies showing that women with unilateral or bilateral oophorectomy had higher risk of cognitive impairment or dementia compared to age-matched women without oophorectomy [19,20]. Estrogen replacement therapy after menopausal showed a neuroprotection effect on cognitive impairment induced by surgical menopause [21,22]. Clinical evidences had also proved further evidence on estrogen-induced cognitive improvement in aged women. For example, Wroolie and his colleagues compared verbal memory between post-menopausal women (>55 years old) with risk factors for AD received 17β-estradiol (E2) and conjugated equine estrogen (CEE). They found that women treated with E2 had better performance in verbal memory test compared to subjects received CEE [23]. A functional magnetic

resonance imaging (fMRI) study revealed that estrogen treatment induced activation in the prefrontal cortex in young women (27–49 years old) with Lupron-induced ovarian suppression underwent estrogen replacement therapy (ERT) compared age-matched Lupron-treated women without ERT. In addition, studies have demonstrated that long-term use of estrogen would increase activation of hippocampal with better performances in verbal and figure memory tests [24,25]. Together, these studies suggested a brain functional improvement by estrogen. However, there were also studies showed limited or no effect of estrogen on cognitive function. For example, another fMRI study showed significant activation in the regions of prefrontal cortex in estradiol-treated women compared with placebo-treated controls during verbal, spatial and visual memory tasks, but only reduced errors of perseveration during verbal recall [26]. The inconsistent in the effects of estrogen on cognitive function might be related by the variation of ERT durations and the specific cognitive tasks. For instance, the verbal memory, a most sensitive variable for women, was not always included. Taken together, prefrontal cortex and hippocampus are the most important brain regions associated cognitive function related to estrogen therapy.

In consistent with human studies, the estrogen-induced cognitive improvement had also been demonstrated in various animal studies [27,28]. It is also reported that the estrogen-induced cognitive improvement has also a brain regional-dependent effect. E2 administration could improve prefrontal cortex and hippocampus associated learning activities in rats while a negative effect of estradiol on the striatum-dependent learning was observed [29,30].

There are several hypotheses of underlying mechanism of estrogen-induced cognitive function improvement. One of the most popular mechanisms is the regulatory effect of estrogen on brain derived neurotrophic factor (BDNF). Many studies have showed that estrogen treatment can ameliorate memory by increasing spine density through elevation of BDNF level [31,32]. Some of the estrogen-induced BDNF neurotrophic effects are estrogen receptor-dependent. Tamoxifen, an estrogen receptor antagonist, decreased BDNF level in mice cerebellar, and BDNF administration increased Purkinje cell growth in these animals [33]. Estrogen receptors are also partially responsible for the estrogen-induced cognitive function improvement. For instance, estrogen receptor α was involved in estradiol enhanced object recognition memory in ovariectomized (OVX) mice [34]. Moreover, injection of ICI 182 780, an estrogen receptor antagonist, into rat hippocampus bilaterally reversed the systemic estrogen administration-induced enhancement in place learning, suggesting that the estrogen-induced enhancement on place learning was dependent on the activation of hippocampal estrogen receptor [35]. Furthermore, various neurotransmitters are also playing roles in estrogen-induced cognitive improvement, such as norepinephrine, dopamine, serotonin, and acetylcholine [36,37]. In addition, epigenetic regulation of estrogen is also an assignable factor in the amelioration of memory. A series of studies have showed that dorsal hippocampal H3 acetylation and DNA demethylation of genes necessary for memory formation including BDNF gene are essential for E2 to enhance object recognition memory consolidation in female mice [38]. There were some reports on estrogen regulating vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1) in both human and animal studies. It is general accepted that estrogen promotes cognitive function partially through activation of VEGF and IGF-1 [39,40], although the effect of estrogen on IGF1

remains controversial which might be associated with the different estrogen administration routs [41] (figure 1).

Cognitive impairment associated with AIs

AIs have been used as an adjuvant therapy for estrogen receptor-positive breast cancer patients by inducing an abrupt reduction of endogenous estrogen levels. As side effects of low endogenous estrogen, AIs can lead to risk of osteoporosis, fractures, cardiovascular disease and cognitive decline [9,11,42,43]. For example, the Intergroup Exemestane Study reported that patients switching to exemestane, one of AIs, had a higher incidence of fractures than those continuing receiving tamoxifen, a selective estrogen receptor modulator (SERM) as 7.0 vs 4.6%; P=0.003 [43]. Cardiovascular events were more common in patients receiving exemestane than those switched to tamoxifen as 20.8 vs 18.9%; P=0.09 [43].

Human studies

Although multiple studies demonstrated cognitive impairment associated with AIs treatment in breast cancer patients, the effect of aromatase on cognitive function by pharmacological inhibition remains controversial. For example, in humans, several studies showed that AIs treatment, a standard therapeutic strategy for women with estrogen receptor-positive breast cancer, showed a significant decline in cognition, particularly in cognitive processing speed and verbal memory [9–11]. One of the studies compared the outcome from cognitive tests performance and self-reported cognitive function in patients treated with AI and SERM, such as exemestane or tamoxifen and healthy controls. The results showed that all patients had significant decline in their objective cognition (two category fluency tests and one information processing speed tests) and subjective cognitive function compared with healthy controls [10]. Similarly, Collins and his colleagues used a longitudinal design to study the effect of adjuvant therapy on breast cancer patient's cognition by conducting a baseline assessment (T1) and a second assessment (T2) after 5–6 months treatment in breast cancer patients and age-matched healthy controls. A significant decline of cognition from T1 to T2 was observed in patients under adjuvant therapy, such as tamoxifen and anastrozole, one of AIs, compared with healthy controls. Among the all cognitive performance tests, the most effected cognitive domains affected by adjuvant therapy were processing speed and verbal memory [9]. Since the plasma estrogen level was much lower in breast cancer patients treated with anastrozole than those received tamoxifen treatment, Bender and his colleagues compared cognitive function between patients received anastrozole and tamoxifen for 3 months, and found that women received anastrozole had poorer visual and verbal learning and memory than those received tamoxifen [44]. In addition, Lejbak et al. demonstrated additional estrogen sensitive cognitive domains, such as letter fluency, complex visuomotor attention and manual dexterity [45].

However, there were also several studies showed no effects of AIs on cognitive function in breast cancer patients [46–49]. For example, Hermelink and his colleagues assessed cognitive function in 101 breast cancer patients (62 treated with tamoxifen, anastrozole or letrozole for average 19 weeks) at the beginning of treatments, the end of treatments and 1 year after the first assesses. They failed to identify any significant effects of anti-estrogen

treatments on patient's cognition tests [46]. This result might be caused by learning effect with the same test conducted twice. Cross-session studies from Breckenridge et al. and Kilickap et al. evaluated cognition among breast cancer patients (aged 33–81) and found the effects of anti-estrogen therapy were distinct for patients at different menopausal status [47,48]. In addition, Hurria and his colleagues examined the relationship between AIs and cognition in 32 breast cancer patients aged >60 years old who had positron emission tomography (PET) scans and found no significant decline in cognition in patients treated with AIs therapy for 6 months compared with age-matched healthy controls. However, there were significant changes in cerebral metabolic activity between the AIs treated patients and healthy controls and the primary effective brain regions involved the medial temporal lobes and Broca's area which are associated with long-term memory and verbal exposition, respectively [50]. This result suggested that AIs therapy might affect cognitive function through dysregulating metabolic activities in associated brain regions. However, the association between PET and cognition in AIs treated patients need further confirmative investigations due to the modest sample size with only 32 patients [50]. Furthermore, studies showed that cognitive function of postmenopausal women with breast cancer improved one year after the anti-estrogen therapy [51]. However, they did not conduct baseline assessment before treatment to get whether patients cognitive function could back to original statement [51].

In contrast, the effect of anti-estrogen therapy on cognition by self-reported cognitive performance were relative consistent. Studies showed that AIs treatment in breast cancer patients caused decline of subjective cognitive function [10,47,52], and such a cognitive impairment persisted for long time after the treatments reported in the follow-up studies [53]. However, studies showed irrelevance between self-reported cognitive functioning and cognitive test performance [10,54] or positive correlation only in the area of verbal memory [55]. The most assessments of subjective cognitive functioning in self-reported studies were the Cognitive Failure Questionnaire which primarily focusing on perception, attention and motor function [10,54,56], while the most AIs effective domain of cognition were verbal memory and information processing speed [9–11]. Therefore, these self-reported studies on subjective cognitive function might reflect partially, but not targeted cognitive impairment in AIs treated breast cancer patients. Bender et al. used the Patient's Assessment of Own Functioning to evaluated perceived cognitive function, and discussed the relevance of objective and subjective cognition in early-stage breast cancer patients receiving adjuvant hormonal therapy (tamoxifen or anastrozole) and found that poorer cognitive function was related to poorer verbal learning and memory [55]. Again, all suggested that the controversial findings of AIs-related cognitive function in human might well be related to the type of cognitive function tests as well as menopausal status and variation of treatment durations.

Animal studies

Inhibition of aromatase induced cognitive impairment has been found in animal studies. Using genetic approaches, studies demonstrated that mice with genetic knockout of aromatase gene (ArKO) performed significant worse in Y-maze test for short-term spatial reference memory than wildtype control mice [57]. It was reported that the number of spine

synapses was significantly reduced in the hippocampus of mice treated with letrozole (one of AIs) compared to wildtype mice [56]. Furthermore, studies of AIs treatment and long-term potentiation (LTP) in the hippocampus demonstrated a reduction in the magnitude of LTP in brain slices from the letrozole-treated animals compared to that from the control mice. And the LTP impairment increased significantly with longer treatment duration in female mice [58]. AIs, particularly letrozole, also could down-regulate steroid receptor coactivator-1 in specific brain regions primarily related to memory and integration [4]. Instead of causing reduction of spine synapse and LTP, some studies found beneficial effects of AIs on cognition. For example, systemic injection of letrozole increased spatial learning and memory activities in rats [59], while other research found an increase in expression of N-methyl-D aspartate (NMDA) receptor in female ArKO mice (14–16 weeks old) with higher performance in water maze test [60]. Moreover, an increased level of catecholaminergic neurotransmitters like noradrenaline and dopamine in the prefrontal and hippocampus after high dose (1mg/kg) of letrozole treatment for 6 weeks in OVX rats, while the level of catecholaminergic neurotransmitters above was decreased in OVX control group and intact letrozole treatment group [59]. These results indicated a potential window of protective action of AIs in OVX mice, not in intact mice.

In conclusion, aromatase deficiency at early age may lead to cognitive impairment while a potential bi-phases effect of AIs has been observed in aged animals. The animal studies are in consistent with human studies that AIs-induced cognitive impairments mostly occur in surgical menopausal women [61]. The impairment of cognition induced by aromatase deficiency might be induced by loss of spine synapse followed by impaired LTP. In addition, NMDA receptor, catecholaminergic neurotransmitters and steroid receptor coactivator-1 may also involve in the aromatase-related cognitive changes.

The possibility of exercise on improving the cognitive impairment induced by AIs

Positive effects of exercise on cognition

Physical activity, as a non-pharmacological therapy to cognitive impairment, has gained more and more attention recently. Numerous studies have confirmed the positive effects of exercise on cognition, especially in elderly adults with moderate cognitive impairment [62–65]. It was reported that multimodal physical training for 16 weeks reduced pro-inflammatory cytokines and improved BDNF peripheral levels, which lead the improvement of cognition in subjects with mild cognitive impairment [66]. Another independent study revealed that healthy adults at age 62–89 years after 12-month coordination exercise had better executive function mediated by the increased volume of basal ganglia nuclei [67]. Physical activity has been associated with better memory function mediated by increasing cerebral gray matter volume in prefrontal and cingulate cortex in healthy elderly adults [68,69]. The beneficial effects of exercise on memory storage and consolidation were also found in preadolescents and young adults [70–72], and this effect might be mediated by enhancing levels of BDNF and catecholamine [70]. Regression analyses showed that the exercise-induced enhancement of cognitive inhibitory control function in healthy young adults might be related to the increased cerebral-blood-flow (CBF) regulation as well as

cerebrovascular function [73,74]. In addition, the positive association between physical activity and cognition improvement were also reported in breast cancer survivors [75]. Because of both people with estrogen deficiency and breast cancer survivors often reported cognitive decline [47], it might be worth to investigate whether exercise could prevent or treat cognitive impairment in breast cancer patients treated with or without AIs. Indeed, Pradhan et al. showed that an exercise for 3 months has great likelihood to provide better attention function in young breast cancer survivors [75].

Animal studies provided further support on cognitive improvement induced by exercise. Studies observed that six weeks of treadmill exercise could protect short-term and spatial memory impairments in aged rats through increasing neurogenesis and suppressing apoptosis in hippocampus [76]. Exercise also can up-regulate proteins related to energy metabolism (i.e. Glycolysis, ATP synthesis, ATP transduction and glutamate turnover) and synaptic plasticity to enhance cognitive function [77]. Furthermore, changes in neurotrophic and growth factors, such as BDNF, IGF-1 and VEGF induced by exercise also contribute important roles the protection of cognition decline [16,78–80]. For example, treadmill exercise of 39 days in early age (21 days old) rats increased mossy fibers density and expression of BDNF and its receptor tropomyosin-related kinase B in hippocampus, which induced the improvement of spatial learning and memory. These exercised-induced enhanced spatial memories were maintained for long which were measured at 96 days old [81]. Blocking the action of BDNF abolished improvement in learning acquisition and increased expression of proteins related to energy metabolism and synaptic plasticity induced by 1-week wheel running [82,83]. IGF-1 can interact with BDNF to participate the action on learning and memory through synaptic plasticity, neurogenesis and energy metabolism [16,84]. Interesting enough, studies showed that the exercise-induced learning and memory improvement would be abolished after blocked of VEGF and IGF-1 respectively [84,85]. Moreover, exercise can ameliorate cognitive function through gene level. For instance, Kohman et al. found that 8 weeks wheel running reversed age-induced decreasing expression of genes involved in cell growth and increasing expression related to immune function [86]. Other evidence also demonstrated that exercise-induced enhancement of learning and memory is partially mediated through facilitating DNA demethylation and acetylation of histone H3 localized to the promoter IV of the BDNF gene, a region intimate related to neuronal activity [87].

In conclusion, exercise can improve cognition through numerous pathways including improving cerebrovascular function, CBF regulation, immune system, stimulating neurotrophic factors and growth factors. The effects of exercise on growth factors-mediated cognitive function are similar to the pathways of estrogen-induced cognitive improvement (Fig. 1).

The interaction of exercise and estrogen on cognition

Clinical observation demonstrated that women with estrogen deficiency often engaged in cognitive impairment. As mentioned above, some of breast cancer survivors who had received AIs therapy also developed cognitive decline compared with healthy controls [9–11]. Higher incidence of AD in post-menopausal women was also reported than that in age-

matched men [88]. Women with surgical menopause at early age have higher risk of AD than healthy age-matched women [17]. While exercise has been widely used for better cognitive function in general, a meta-analysis revealed that the exercise-induced beneficial effect was more effective in females than males [64]. Furthermore, Jianqiang and his colleagues reported that 2-months treadmill increased serum levels of estrogen and level of BDNF in the rats hippocampus [89]. An independent study also found that 30 days of treadmill running in OVX rats could restore estrogen deficiency-induced down-regulation of creatine kinase activity, an important enzyme in energy metabolism [90]. To investigate the effect of exercise on estrogen deficiency-induced impairment of memory and cognition, Juliana Ben and his colleagues examined roles of running on female Wistar rats at 3 months old with or without ovariectomy. The exercise was conducted as running in a moderate intensity three times per week for one month. They found that OVX mice demonstrated a significant impairment in the inhibitory avoidance and Morris Water Maze test compared to the shamed mice, while exercise can restore the inhibitory avoidance behavior and spatial navigation memory in the OVX mice [91]. Another study showed that exercise reversed the estrogen deficiency-induced increased activation of Na^{+}, K^{+}-ATPase and acetylcholinesterase in hippocampus and cerebral cortex in OVX mice [92]. All together suggested that exercise not only increase cognitive performance in general, but also protects the estrogen deficiency-induced cognitive decline in females.

However, the effect of exercise on estrogen deficiency-induced cognitive decline may be dependent on the length of exercise as well as the duration of estrogen deprivation. Studies showed that levels of BDNF mRNA in the hippocampus were lower in rats with ovariectomy for long term (7 weeks) than short term (3 weeks). Five days wheel running restored BDNF gene expression in short-term estrogen-deprivation rats only, suggesting that long term absence of estrogen might change the threshold to trigger a BNDF gene response, which leading a limitation for exercise in OVX rats with long term estrogen deficiency [93]. Evidence from Moreno-Piovano confirmed this speculation. Moreno-Piovano and his colleagues found higher methylation levels of regulatory sequences of BDNF in long-term OVX mice compared with short-term ones. In addition, estradiol failed to increase BDNF expression after long-term estrogen deficiency, while estradiol exerted an ideal effect on increasing BDNF and synaptophysin protein expression [94]. Similarly, Marosi and his colleagues compared the effects of E2 and long term moderate exercise on cognitive function and related intracellular molecular signaling pathways and found while E2 and exercise alone both enhanced attention and memory and activation of PKA/Akt/CREB and MAPK/CREB pathways in female rats at 15 months old, exercise alone failed to ameliorate behavior and molecular mechanism in female rats at 27 months old. In addition, E2+exercise improved cognitive function with enhanced activation of relevance pathways both in rats at 15- and 27-month of age [95]. Therefore, these data suggested that exercise may share similar beneficial effects on cognition and combination of exercise with estrogen treatment might play provide more power in improving cognitive function, particularly in aged females.

Conclusions

Estrogen is very important in the regulation of cognitive function. Lack of estrogen like aromatase inhibitor treatment among breast cancer patients might cause cognitive impairment. Exercise is an effective intervention to improve cognitive function. This improvement is more significant among persons with cognitive disease. Numerous evidences revealed that exercise and estrogen have many common ways in the regulation of cognitive function. Therefore, it is provided an opportunity for exercise to ameliorate cognitive decline induced by AIs treatment in breast cancer patients.

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Abbreviations

AIs	Aromatase inhibitors
AD	Alzheimer’s disease
E2	17β-estradiol
CEE	Conjugated equine estrogen
fMRI	Functional magnetic resonance imaging
ERT	Estrogen replacement therapy
BDNF	Brain derived neurotrophic factor
OVX	Ovariectomized
SERM	Selective estrogen receptor modulator
PET	Positron emission tomography
ArKO	Knockout of aromatase gene
LTP	Long-term potentiation
NMDA	N-methyl-D aspartate
CBF	Cerebral-blood-flow
IGF-1	Insulin-like growth factor-1
VEGF	Vascular endothelial growth factor

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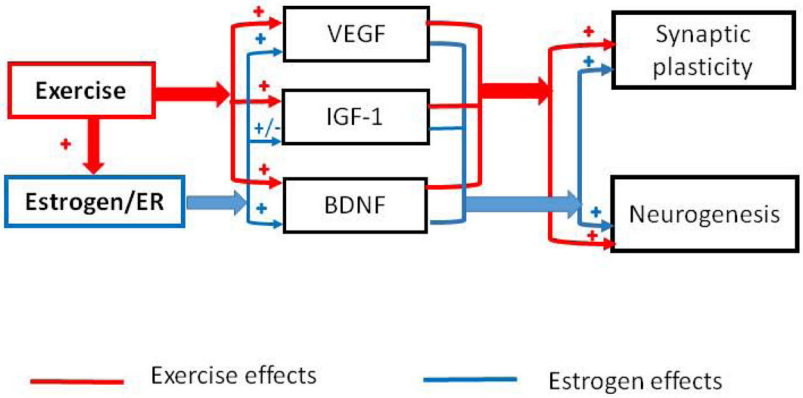

Fig. 1. The relationship of mechanisms between exercise- and estrogen- induced neuroprotection

Exercise can facilitate neuroplasticity and neurogenesis through improving the expression of VEGF, IGF-1, BDNF as indicated as red lines, while the effects of estrogen on cognitive function might be mediated through estrogen receptors and regulate VEGF, IGF-1 and BDNF to exert neuroprotective functions as shown in blue lines.