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Physical exercise prevents cognitive impairment by enhancing hippocampal neuroplasticity and mitochondrial function in doxorubicin-induced chemobrain

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ABSTRACT

Although chemotherapy increases the survival rate of patients with various cancers, such treatment can induce acute or long-term cognitive dysfunction a phenomenon known as post-chemotherapy cognitive impairment (PCCI) or "chemobrain." Exercise is known to positively affect brain function. Thus, the present study aimed to determine whether symptoms of chemobrain and disruptions in the neuroplasticity and functioning of hippocampal mitochondria can be prevented or relieved by exercise. Wistar rats were separated into the following groups: control, control plus exercise, chemobrain, and chemobrain plus exercise. For chemobrain induction, 2 mg/kg of doxorubicin (DOX) a widely utilized chemotherapeutic agent among patients with breast cancer was dissolved in saline and directly injected to the abdomen once every 4 weeks. The exercise groups were subjected to low-intensity treadmill, 6 days per week for 4 weeks. The Morris water maze and step-down avoidance tests were conducted to evaluate cognitive function, while neuroplasticity and mitochondrial function were assessed in the hippocampus and dentate gyrus. Decreased cognitive function were observed in the chemobrain group, along with decreases in levels of neurogenesis, brain derived neurotrophic factor (BDNF), tropomyosin-related kinase B (TrkB), Ca^{2+} retention in hippocampus. Rats of the chemobrain group also exhibited an increase in apoptosis, H_2O_2 emission and permeability transition pore by hippocampal mitochondria. However, exercise attenuated impairments in cognitive function, neuroplasticity, and mitochondrial function induced by DOX treatment. Therefore, the findings of the present study indicate that low-intensity exercise may assist in preventing cognitive dysfunction during or after chemotherapy in patients with various cancers, including breast cancer.

1. Introduction

Although the incidence of various cancers has increased worldwide, the survival rate of patients with cancer has also increased due to advancements in medical technology, diagnostic methods, and treatment. While systemic chemotherapy is pivotal in the treatment of various forms of cancer (Ahles and Saykin, 2002), chemotherapy can induce acute or long-term cognitive side-effects such as dysfunction in memory, concentration, reasoning, executive function, and visuospatial skills during or following treatment (Meyers, 2000; Olin, 2001). The phenomenon in which cognitive dysfunction develops during or following chemotherapy is referred to as post-chemotherapy cognitive impairment (PCCI) or "chemobrain" (Nelson et al., 2007).

Interestingly, previous studies have indicated that survivors of breast cancer report higher rates of dysfunction in memory and concentration following chemotherapy than those with other forms of cancer (Fardell et al., 2011). Although the chemotherapeutic agent doxorubicin (DOX) which is commonly utilized in patients with breast cancer cannot pass the blood brain barrier (BBB), brain toxicity induced by DOX can indirectly lead to the production of toxins. DOX stimulates the production of tumor

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necrosis factor alpha (TNF-α), which in turn induces the release of inflammatory cytokines from microglial cells in the brain. The resulting increase in TNF-α production enhances the production of reactive oxygen species (ROS) (Tacar et al., 2013) and inhibits adult neurogenesis by up to 50% in the hippocampus (Monje et al., 2003). According to a study by Tangpong et al. (2006), animals treated with DOX exhibit increases in TNF-α level in the hippocampus and cortex. Increased TNF- α in the hippocampus causes memory impairment and hippocampal dysfunction (Ren et al., 2011). Chamberlain et al. (2013) reported that DOX induces significant toxicity, when it is attached to a peptide that targets mitochondria.

Several recent studies have reported that cognitive dysfunction occurs following various chemotherapy procedures in patients with breast cancer (Kesler et al., 2013; Piccirillo et al., 2015; Vance et al., 2017). Various studies have revealed that impairments in memory are particularly common among patients with breast cancer who have received chemotherapy (Ahles et al., 2002; Falleti et al., 2005; Tager et al., 2010), and that many female survivors of breast cancer experience difficulty performing work at their previous level of proficiency (Munir et al., 2011). Memory, which refers to the psychological process during which an individual's experience is accumulated and stored, plays an important role in the overall cognitive function in humans (Cheng et al., 2013). Thus, memory dysfunction may substantially impact quality of life in patients with breast cancer (Pinto and de Azambuja, 2011).

The hippocampus, which plays a key role in learning and memory, represents the primary site of neurogenesis in adulthood and thus exhibits the greatest potential for neuroplasticity in the brain (Fuchs and Gould, 2000; Lie et al., 2004). Neuroplasticity of the hippocampus can be influenced by the activity of neurotrophic factors, such as brain derived neurotrophic factor (BDNF) (Griffin et al., 2009; Marlatt et al., 2012). BDNF plays an important regulatory role in the maintenance, growth, survival, and formation of neurons (Mattson et al., 2004). BDNF also binds to tropomyosin-related kinase B (TrkB) to exert anti-apoptotic effects (Almeida et al., 2005).

The main functions of mitochondria in neurons involve the control of Ca^{2+} uptake, redox signaling, developmental and synaptic plasticity, and cell survival and death (Mattson et al., 2008). Furthermore, the mitochondrial permeability transition pore (mPTP), which is closely associated with apoptosis, exhibits various physiological functions at the cellular level and plays an important role in learning and synaptic plasticity (Pfeiffer et al., 2001; Weeber et al., 2002). Thus, impairments in mitochondrial function and signaling may be associated with dysfunctional neuroplasticity and various neurodegenerative diseases (Cheng et al., 2010). In particular, mitochondria in the hippocampus may play key roles in the fundamental cellular processes underlying neuroplasticity.

Accumulating evidence has indicated that exercise relieves stress and anxiety to enhance mental and physical health. Physical activity induces neuronal and biochemical changes in the brain that activate neurotransmitters and induce gene expression, which drives the proliferation and survival of neurons in the brain (Stummer et al., 1994), maintains and enhances cognitive function, and confers neuroprotection against brain damage (van Praag et al., 1999 a; Stummer et al., 1994). Therefore, the current study aimed to determine whether symptoms of chemobrain, cognitive dysfunction, neuroplasticity, and mitochondrial function in the hippocampus can be impaired by DOX, and whether such impairments can be prevented or attenuated by exercise.

2. Maternal and methods

2.1. Animals

All animal experimental procedures conformed to the regulations stipulated by the National Institutes of Health (NIH) and the guidelines of the Korean Academy of Medical Science. This study was approved by the Kyung Hee university Institutional Animal Care and Use Committee (Seoul, Korea) (KHUASP (SE)-15-086). The rats were housed under controlled temperature (20 ± 2 °C) and lighting (07:00 to 19:00 h: The light period started at 7 a.m.) conditions with food and water available *ad libitum*. Male 6 weeks old Wistar rats were randomly divided into 4 groups (n = 15 per group): control (CON), control plus exercise (CON + EX), DOX-induced chemobrain (CHEMO), and DOX-induced chemobrain plus exercise (CHEMO + EX). BrdU (Sigma, St. Louis MO, USA) at 100 mg/kg/day was administered intraperitoneally (i.p.) for sequential injections for 7 days in the first week of exercise were given 4 weeks prior to the sacrifice to observe neurogenesis. Behavioral analysis and training were conducted upon the completion of all treatments.

2.2. Chemobrain induction

To develop the experimental animal model utilized in the present study, 2 mg/kg of DOX was dissolved in saline and directly injected into the abdomen of rats once every 4 weeks. In order to maintain hydration and avoid appetite stimulation and excessive weight loss following DOX injection, Recovery diet gel (ClearH_2O) was provided every other day (Christie et al., 2012). DOX was purchased from Tokyo Chemical Industry (Tokyo, JAPAN).

2.3. Exercise protocol

The exercise group began their exercise on a treadmill made for animal use. For the exercise, 5 min of warm up at a 0° inclination at 3 m/min, 30 min of the main exercise at 10 m/min, and 5 min of cool down at 3 m/min were performed. The exercise was performed once a day and six days per week for 4 consecutive weeks. During treadmill running, electrical stimulation was removed to minimize stress. Non-exercise group was set free on the rail while the treadmill was non-operational for the same duration of exercise time as in exercise group.

2.4. Behavior test

2.4.1. Morris water maze

Spatial learning and working memory was evaluated with the Morris water maze task. This task requires rats to learn the spatial location of a hidden platform in a black circular pool (180 cm in diameter and 50 cm high) filled with clear water (25 ± 1 °C). The hidden platform (15 cm in diameter and 40 cm high) was placed 2 cm below the surface of water in the middle of the north quadrant and was camouflaged by virtue of being transparent against a black background. Distal visual cues were placed on the walls around the pool. The position of the cues remained unchanged through the task. One day before training, rats were habituated to swimming for 60 s in the pool without a platform. All rats were trained four times a day for five consecutive days and 24 h after the last training, probe trail was conducted. When finding the platform, rats were allowed to remain for 30 s. If rats did not find the platform within 60 s, they were guided by hand to the platform. Rats were given 60 s retention probe test, and then the platform were removed from the pool. Data were automatically collected via the Smart Video Tracking System (Smart version 2.5, Panlab, Barcelona, Spain).