

Benefits of Physical Exercise for Individuals with Fragile X Syndrome in Humans

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Fragile X syndrome (FXS) is the most common known genetic cause of autism spectrum disorder, and is also linked to other neurologic and psychiatric disorders. The purpose of this review article is to examine a variety of recent studies on the correlation between physical exercise and autistic behavior in individuals with fragile X syndrome. Additionally, we discuss promising approaches for further investigation of the benefits of physical exercise for autism spectrum disorder (ASD) patients. A systematic search of the PubMed digital library database for pertinent articles published from 1995 to 2011 was conducted. Individuals with ASD who experience exercise tend to exhibit improvement in physical function. In addition, exercise promotes neurotrophic factors and boosts the growth of new brain cells. The collected review articles describe how physical exercise has particular effects on stereotypic behavior and cognition among ASD patients. Finally, physical exercise may benefit patients with autism spectrum disorder through the improvement of muscular strength for increased physical capability.

Key Words: Autism spectrum disorders, Fragile X syndrome, Physical exercise

INTRODUCTION

Fragile X syndrome (FXS) is the most frequent form of inherited intellectual disability, and is the most common known cause of autism or autism-like behaviors [1]. This syndrome shares clinical behavioral features with mental retardation, learning disorders, attention deficit disorder, hyperactivity disorder, anxiety, and epilepsy [2-4]. Recent

studies report an association between the therapeutic potential of physical exercise and autistic individuals with fragile X syndrome. Physical exercise as an aspect of autism therapy could lead to increased neuronal survival and counter brain injury in ASD patients [5,6]. In addition, a variety of activities ranging from light leisure activities to heavy aerobic exercise promotes brain vascularization and stimulates neuronal and glial genesis [7]. Exercise also enhances memory and cognitive functions [8,9]. Some studies report that specific molecular factors contribute in multiple ways to the beneficial effects of exercise on brain function in patients with autism-like diseases [10-12]. Neurotrophic factors, such as nerve growth factor (NGF), fibroblast growth factor 2 (FGF-2), and brain-derived neurotrophic factor (BDNF) are generated in the hippocampus in response to exercise [13,14]. Thus this review discusses the effects of physical exercise intervention on stereotypic behavior and physical

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capability in people with ADS.

A systematic search of articles and review papers in the PubMed digital library database from 1995 to 2011 was conducted. The criteria of the article search mainly focused on physical exercise correlated with autism spectrum disorder. Only papers published in English in international journals were adopted for this study. The main key search words were physical exercise, rehabilitation, and autism spectrum disorder. Additionally, we inserted some synonyms of autism-like diseases to search a greater number of articles containing more and deeper results for the present review.

EFFECTS OF PHYSICAL EXERCISE ON MOVEMENT AND BEHAVIORAL IMPROVEMENT IN AUTISM

Individuals with ASD tend to have balance problems in gait, posture instability, and difficulties in joint flexibility. In addition, they have deficits and delays in the development of motor behaviors [15-20]. These difficulties in motor abilities may be further impaired by reduced opportunities to engage in physical exercise and behavioral intervention. The physical exercise of children with autism alleviates the symptoms of autism [21]. Moreover, game exercise that combines physical and mental activities has decreased stereotypies in individuals with autism and has improved their cognitive function [22]. In the case of aerobic exercise, improved academic function has been found in children with ASD [23]. In addition, enhanced motor ability and sensory integrative function due to physical activity may be consistently maintained in patients with ASD [24]. The difficulties that arise in community interactions with ASD mainly pertain to the lack of understanding that results from an incapability to effectively interpret ASD behaviors. Physical exercise is confirmed to be an effective means to prevent these problems between general and ASD populations. Mild exercise programs involving walking and jogging decrease stereotypic behaviors in the short term, but this state of behavior is shown to return to previous levels after 90 minutes following the exercise. Exercise may provide important feedback for self-stimulatory behavior in children with ASD [25]. Some studies confirm that walking exercise not only improves the physical condition, but also

reduces the BMI (body mass index) of patients with severe autism. Following physical exercise, stereotypic and maladaptive behaviors in ASD patients have been shown to improve, and sleep disorders and physical capabilities involving muscular strength have also been enhanced [26].

PHYSICAL EXERCISE AND NEUTROPHIC FACTORS

Stimulation of the fragile X mental retardation 1 (FMR1) gene at postsynaptic sites is associated with the neuronal plasticity of dendritic spines [27]. Therefore, an absence of FMR1 genes is expressed in neuronal dysmorphology and the defection of dendritic spines. A great deal of evidence suggests that synaptic dysfunction is a cause of autism [28]. Some research points out that autism is characterized by the disruption of synaptic pathways caused by a rare mutation [7]. In fact, the disturbance of synaptic pathways may affect neuronal survival. Neurotrophic factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), fibroblast growth factor 2 (FGF-2), and other molecules contribute to synaptic transmission. Moreover, neurotrophic factors play a role in the regulation of synaptogenesis, synaptic plasticity, and neural survival [9]. Physical exercise promotes cerebrovascular activity and activates neurotrophic factors [10]. Studies show that synaptic plasticity, neurotransmission, and neural growth factor are increased in rat and mouse brains due to physical exercise [11]. Brain-derived neurotrophic factor (BDNF) binds to receptors *trkB* and *p75NTR*, resulting in the regulation of neuronal differentiation and survival in embryos [29]. In adults, BDNF may be necessary for both the proliferation and long-term survival of newborn neurons in the forebrain [30,31]. These neurotrophic factors tend to increase with physical exercise, and expression of BDNF is reported in parts of the brain—particularly the hippocampus—as a result of physical activity. It is suggested that exercise increases levels of neurotrophic factors in the brains of humans [12]. The current study confirms the important role played by BDNF in ASD [13]. Levels of BDNF may be a factor in clinical diagnosis and intervention for the pathophysiology of autism in patients. Previous studies show that BDNF levels in autism patients under six years of age are significantly

higher than BDNF levels in autism patients over six years of age. One study shows a negative association between expression of BDNF and age [31]. ASD reduces volume in the forebrain, including the size of the amygdala and hippocampus, relative to total brain volume. This finding reflects the neural connections of limbic systems with other parts of the cerebral cortex [32]. On the other hand, exercise has been associated with increases in hippocampal tissue, and with boosting the growth of new brain cells by increasing BDNF in the brain cortex [33]. It is probable that the growth of new brain cells in the hippocampus, together with the modulation of remaining connections in the brain cortex are responsible for improvements in brain function due to physical exercise.

CONCLUSION

The field of autism is linked with extensive research in areas of molecular biology and has infinite potential for targeted treatment. This study highlights a variety of beneficial neurological effects of physical therapy in autism. Our review researches the characterization of autism and investigates preventive and therapeutic approaches to FXS in ASD. We explore the clinical application of physical exercise-based therapeutics, leading to effective treatment and clear benefits in the prevention of disease. However, additional studies are needed to examine the mechanism of melatonin associated with autism and FXS. As a result of the positive influence of exercise, neurotrophic factors and the growth of new brain cells are activated for increased physical capability. Further research is required to investigate the mechanisms of interaction between improvement due to exercise therapy for various ASD behaviors and newly generated brain cells through increased neurotrophic factors.

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