EXERCISE AND SYMPTOMS OF ALZHEIMER'S DISEASE: WHAT HAS BEEN KNOWN SO FAR?

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ABSTRACT

Clinical studies in persons with Alzheimer's disease (AD) reported severe decrements in cognitive functions and reduced cerebral blood flow or cerebral glucose utilization rate compared with age matched healthy counterparts. These derangements produce the clinical symptoms of AD. However, exercise has been widely reported to induce a number of growth factors: BDNF, IGF-1 and VEGF which enhance brain health through neurogenesis, plasticity and angiogenesis. Yet, the saddest point is that, despite this breakthrough in clinical sciences, only few of these patients benefit from this intervention. Therefore, a literature review like this is very necessary to delineate the rationales and effectiveness of exercise intervention in Neurodegenerative conditions like the Alzheimer's disease.
Keywords: Exercise, Alzheimer's disease, symptoms

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive decline in memory, judgment, ability to reason, and intellectual function which is accompanied by a wide range of neuropathologic features including extracellular amyloid plaques and intra-neuronal neurofibrillary tangles (Das & Lal, 1997). However, the cause of AD is obscure and no cure is as yet available. But, there are risk factors for the disease which include: defective genes on chromosomes 1, 14, 19 and 21, the apolipoprotein E4 (apoE4) variant (which brings the age of onset forward), insulin resistance, increasing age, positive family history, low education level, history of head trauma and cardiovascular disease (Longmore et al, 2004 & Van Duijin et al, 1991). The amyloid precursor protein shows selective neurotoxicity to hippocampus and entorrhinal cortex and usually spares the cerebellar cortex. The majority of cases (90-95%) are sporadic, while the remaining 5% is familial (Goerdart et al, 1994). Most familial AD cases are caused by mutations in the gene for presinilin 1 (PS1) on chromosome 14, some by mutations in the gene for presinilin 2 (PS2) on chromosome 1, while a few have mutations in the gene for amyloid precursor protein (APP) on chromosome 21 (Goedert et al, 1994, Schellenberg et al, 1992, Levy-Lahad, 1995 & Goate et al, 1991). However, to date, there is not a consensus on the hypotheses regarding pathogenesis of AD (Editorial, 1998; Gasparini et al, 1998; Selkoe, 1999 & Yakner, 1996a). But, major emphasis has been placed on the role of amyloid (Selkoe, 1999; Yakner, 1996a; Hardy & Higgins, 1992; Yakner, 1996b, Selkoe, 1997 & Dickson, 1997).

Clinically, this condition presents with memory/ cognitive decline, behavioural changes (e.g, aggression, wandering and disinhibition), hallucination, delusions, apathy, depression, irritability and euphoria (Longmore et al, 2004). The cognitive impairment is progressive, but the behavioural/ psychotic symptoms may go after a few months or years. Towards the end, often but by no means invariably, patients become sedentary, taking little interest in anything. Parkinsonism, wasting, mutism, incontinence ± seizures may occur. The mean survival is 7 years from the disease onset. . However, a variety of specific interventions that improve the symptoms of the condition exercise inclusive, exist.

EXERCISE AND ALZHEIMER'S DISEASE

The benefits of exercise have been best described for learning and memory, protection from neurodegeneration and alleviation of depression, particularly in elderly population (Carl et al, 2007). Exercise increases synaptic plasticity by directly affecting synaptic structure and potentiating synaptic strength and by strengthening the underlying systems that support plasticity including neurogenesis, metabolism and vascular function. Such exercise induced structural and functional change has been documented in various brain regions but has been best studied in the hippocampus. A key mechanism mediating these broad benefits of exercise on the brain is induction of central and peripheral growth factor cascades, which instruct downstream structural and functional change. In addition, exercise reduces peripheral risk factors such as diabetes, hypertension and cardiovascular disease, which converge to cause brain dysfunction and neurodegeneration. A common mechanism underlying the central and peripheral effects of exercise might be related to inflammation, which can impair growth factor signaling both systemically and in the brain. Thus, through regulation of growth factors and reduction of peripheral and central risk factors, ensures successful brain function (Carl et al, 2007).

Evidence indicates that physical and mental activity influence the aging process although only limited research is available (Churchill et al, 2002). In humans, robust effects of exercise have been most clearly demonstrated in aging populations, where sustained exercise participation enhances learning and memory, improves executive function, counteracts age related and disease related mental decline and protects against age related atrophy in brain areas crucial for higher cognitive process (Colcombe & Kramer, 2003). Human data show that executive functions of the type associated with frontal lobe and hippocampal regions of the brain may be selectively maintained or enhanced in humans with higher levels of fitness. There is now a body of literature that suggests that a lifetime of exercise can result in enhancements in a number of aspects of cognition. Much of this literature has focused on aerobic exercise such as walking, running, bicycling and swimming. Similarly, enhancement performance is observed in aged animals exposed to elevated physical and mental demand and it appears that the vascular component of the brain response may be driven by physical activity, whereas, the neuronal component may reflect learning. Recent results have implicated neurogenesis, at least in the hippocampus as a component of the brain response to exercise, with learning enhancing survival of these neurons. Non-neuronal tissues also

respond to experience in the mature brain, indicating that the brain reflects both its recent and its longer history of experience (Carl et al, 2007).

According to Mills et al (2000), depression shows a significant improvement with exercise. Physical activity affects cognitive ability through improvement in learning speed, information processing speed, spatial memory, reaction time, performance on neuropsychological tests, reduction in the risk of cognitive loss and dementia and rate of memory loss (Hillman et al, 2003; Winter et al, 2007; Pereira et al, 2007 & Dick et al, 2003). O' Callaghan et al (2007) and Liu et al (2008), in studies in mice and rats reported that, exercise improves performance in hippocampus-dependent tasks, spatial memory, solving mazes and novel object recognition. Adlard et al (2005) found that, in transgenic mouse model for AD, exercise started before disease onset improved learning and reduced β- amyloid plaques in both hippocampus and cortex. While exercise started after disease onset improved both working and reference memory in aged AD mutant mice (Nichol et al, 2007).

In humans, physical activity protects against brain damage caused by stroke (Guo et al, 2008) and promotes recovery after brain injury (Griesbach et al, 2008). Physical activity is also antidepressant (Lawlor & Hopker, 2001; Delay, 2008 & Deslande, 2009). Bayler & Spirduso (1988) reported benefits of aerobic exercise on both peripheral and central components of reaction. In a review of the effects of exercise on depressive symptoms in 58 randomized trials involving almost 3000 subjects by Rethorst et al (2009), it was found that, participants in the exercise treatment had significantly lower depression scores than those receiving the control treatment. Aerobic physical activity increases oxygen flow to the brain, increases capillary growth which results in increased supply of oxygen and glucose, increased vascular endothelial growth factor (plasticity), muscles produce insulin like growth factor -1 (IGF-1) that enters the brain to cause release of Brain derived neurotrophic factor (BDNF), stimulates production of N-methyl-D-aspartic acid (NMDA), increases neuron growth and plasticity, stimulates hippocampus neuroregeneration, increases expression of genes required for plasticity and increases long term potentiation (LTP) for learning (Cotman et al, 2007 & Hillman et al, 2008).

Clinical studies in patients with Alzheimer's disease, senile dementia, or Huntington's disease have found both severe decrements in cognitive functions and a reduced resting cerebral blood flow or cerebral glucose utilization rate in patients with AD compared with age matched healthy counterparts (Bertsch et al, 2009). Intervention studies demonstrate that, individuals with AD who exercise show improved function and decreased depressive symptoms as compared with non-exercisers who show continued decline (Teri et al, 2003; Stevens & Killeen, 2006). Recent evidence suggests that, exercise might have the most cognitive benefits in individuals with the APOE4 genotype (Rovio et al, 2005) although this area remains controversial (Podewils, 2005). In parallel with clinical studies, exercise has been shown to improve function in several animal models of neurodegenerative diseases by, for example, delaying symptom onset and slowing cognitive decline in mice transgenic for

Huntington's disease (Pang, 2006) and improving spatial learning and memory in transgenic mouse models of AD (Adlard, 2005).

HOW DOES EXERCISE AFFECT OUR BRAIN?

Exercise modulates brain function in many ways. This includes neurogenesis, enhanced CNS metabolism and angiogenesis. However, neurogenesis and other exercise-induced alterations in neuronal circuitry and function must be met with an adequate nutrient and energy supply which in turn is supported by changes in metabolic function and blood flow (Carl et al, 2007). Yet, at first glance, it may seem unlikely that common mechanisms could mediate the varied effects of exercise on learning, depression, neurogenesis, angiogenesis and overall brain health. An emerging overacting concept, however, is that exercise increases brain availability of several classes of growth factors that modulate nearly all of the functional end points enhanced by exercise. BDNF, IGF-1 and VEGF are the principal growth factors known to mediate the effects of exercise on the brain (Carl et al, 2007). But, these growth factors work in agreement to produce complementary functional effects, modulating both overlapping and unique aspects of exercise related benefits in brain plasticity, function and health. The effects of exercise on learning and depression are predominantly regulated by IGF-1 and BDNF, whereas exercise-dependent stimulation of angiogenesis seems to be regulated by IGF-1 and VEGF.

According to Cotman & Berchtold (2002), in animal studies, exercise increases BDNF in several brain regions, and the most robust and enduring response occurs in the hippocampus. Berchtold et al (2005) reported that, after several days of exercise, BDNF gene and protein production by neurons is increased in all hippocampal sub-fields, and remains higher for weeks with sustained exercise. Regulation of hippocampal BDNF by exercise is mediated by neurotransmitter system (Cotman & Berchtold, 2002) and by IGF-1 (Ding et al, 2006). Like BDNF, IGF-1 gene expression is increased in hippocampal neurons in response to exercise, occurring several days after exercise onset. Interestingly, much evidence indicates that, there are points of convergence between IGF-1 and BDNF signaling. Firstly, IGF-1 increases BDNF in response to exercise. Therefore, blocking IGF-1 signaling in vivo prevents the induction of hippocampal BDNF in response to exercise, and in parallel, attenuates the exercise-dependent induction of synaptic proteins (e.g. synapsin 1) downstream from Tropomyosin-Related Kinase B (TrKB) signaling (Ding et al, 2006). Secondly, IGF-1 increases neuronal levels of TrKB in hippocampal cultures, thereby increasing BDNF signaling (McCusker, 2006)-an effect that might also occur in vivo. Thirdly, BDNF, but not IGF-1, modulates the exercise dependent enhancement of synaptic plasticity mechanisms that are thought to underlie learning and memory. For example, BDNF similar to exercise facilitates long term potentiation (LTP) and activates Mitogen-activated protein kinase (MAPK) (Black et al, 1990; Zheng & Quirion, 2004)-a signal transduction pathway that is important for LTP.

Based on observation, hippocampal infusion of BDNF or overexpression of TrKB receptors produces antidepressant-like effects in preclinical models of despair (Koponen, 2005 &

Shirayama, 2002), whereas mice lacking BDNF show impaired anti-depressant response (Monteggia et al, 2004). Similar to BDNF, antidepressant effects have been reported for IGF-1: ventricular IGF-1 injection produces antidepressant-like (anxiolytic) effects that endure for a week or more (Vaynman et al, 2004). Fortunately, these growth factors are induced in response to exercise. Although, the evidence for IGF-1 is not as compelling as that for BDNF, increases in both of these factors in the CNS might contribute to anxiolytic or anti-depressant benefits of exercise. The mechanism by which growth factors might have anti-depressant effects is largely unknown. It has been recently proposed however, that neurotrophic factors themselves do not control mood, but rather they facilitate the activity-dependent modulation of networks that are required to induce antidepressant effects (Castren et al, 2007). It is known that exercise controls signal transduction pathways and gene expression, which then effects downstream change. For example, exercise can activate the MAPK and phosphatidylinositol 3-kinase (PI3K); these pathways can augment LTP and production of additional growth factors. In addition, exercise regulates activity of transcription factors such as cAMP response element binding (CREB) (Shen et al, 2001), which is crucial for learning and memory. Furthermore, proteomic and microarray analyses have shown that, many classes of proteins in addition to growth factors are regulated by exercise (Ding et al, 2006b & Tang et al, 2001), including those involved in metabolism, inflammation and synaptic plasticity. Lastly, exercise through gene and protein expression controls proliferation of various types of cell in the CNS, including neuronal progenitors, glial and epithelial cells. The interactive effects of IGF-1 with VEGF are increased in the periphery by exercise and cross the blood-brain barrier to enter the brain (Trejo et al, 2001; Fabel et al, 2003 & Lopez-Lopez et al, 2004). Peripheral sources of IGF-1 and VEGF mediate stimulation of neurogenesis and angiogenesis with exercise, as has been demonstrated by using blocking antibodies.

Discussion

Alzheimer's disease is characterized by progressive cognitive decline, memory impairment, behavioural changes, depression, euphoria, hallucination, apathy, irritability and delusion (Longmore et al, 2004). These symptoms greatly interfere with the Activities of Daily living. It reduces quality of life and the affected persons may have a mean survival of 7 years from the disease onset (Longmore et al, 2004). However, according to Carl et al (2007); Cotman et al (2007); Hillman et al (2008); Lawlor & Hopker (2001); Mills et al (2000); Nichol et al (2007) and Rethorst et al (2009), exercise is known to induce a variety of growth factors that enhance brain health by improving cognition, depression, long term potentiation (LTP) etc. These growth factors include BDNF, IGF-1 and VEGF. These effects are achieved through neurogenesis, plasticity and angiogenesis. Unfortunately, this intervention is not usually utilized especially in the developing countries where only a few Neuropsychiatric patients are referred for exercise. Combining exercise intervention with other interventions may yield a greater improvement in Alzheimer's disease symptoms. I therefore hope that, this article will serve as reference point and a consciousness raiser to avail our patients with this easily affordable treatment (exercise) for Alzheimer's disease and related neuropsychiatric dysfunctions.

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