(continued from page 18)

Schiller JS et al. Early release of selected estimates based on data from the January-June 2014 National Health Interview Survey, National Center for Health Statistics. http://www.cdc.gov/nchs/data/nhis/earlyrelease/earlyrelease201412.pdf

White House Conference on Aging 2016, Final Report. http://www.whitehouseconferenceonaging.gov/2015-WHCOA-Final-Report.pdf

Dr. Steven C. Castle, MD

Dr. Steven C. Castle, MD is a Professor of Geriatric Medicine at UCLA, Clinical Director of Geriatrics at the VA Greater Los Angeles, and is a Governor appointee to the California Commission on Aging. He is also the first physician to be certified as a FallPROOFTM Instructor from Cal State Fullerton.

His undergraduate degree is from Miami University and he attended Ohio State School of Medicine. He did his residency in Internal Medicine at Riverside Methodist Hospital in Columbus, Ohio and a Geriatric Medicine Fellowship at UCLA.

He has received over $2.8 million in total grant funding, including 2 grants from the NIA; for studies on the immune function with aging, and a collaborator on grants from NIA and NSF for developing protective headwear to reduce brain injury in older adults, as well as mobility and balance awareness programs in affordable retirement communities. He has over 60 publications and has over 400 invited presentations nationally and internationally.

Dr. Castle is also President and CEO of DrBalance, Inc; a web-based platform to provide solutions for mobility and balance changes in older adults across the healthcare spectrum.

He has received many awards and honors, including the Clinician of the Year from the American Geriatrics Society, six teaching awards at UCLA and an Advocacy Award for his work in falls prevention from the James A. Haley VA in Tampa, Fl.

scastle@gravity-happens.com

The Neuroprotective Role of Exercise

Jennifer Voorlas, MSG, CMC

Exercise and Dementia | by Steven C. Castle, MD

The White House Conference on Aging (WHCOA) not only addressed the importance of addressing Alzheimer's and related dementias as a national priority, but also identified The National Institute of Health's "stepped up effort" to find more effective ways to treat and prevent this devastating illness (1).

Jennifer Voorlas has provided a very detailed survey on the neuroprotective role of exercise in brain health for older adults. While there are many supplements being marketed to improve cognitive function as we age, and we hear advertisements for "brain exercises" regularly on the radio, there is more evidence to support that exercise has a much more important role in both the prevention and slowing progression of dementia, including Alzheimer's Disease.

In prevention of dementia, lack of physical activity is the most modifiable risk factor for Alzheimer's Disease in the United States, in addition to beneficial effects on midlife obesity. Regular exercise has demonstrated improved cognition with normal aging outside of dementia. This physiologic improvement in cognition is hypothesized to be due to the beneficial adaptations in vascular physiology and improved neurovascular coupling.

Introduction

Does physical exercise provide an ameliorative effect on age-related neuronal loss? This is a complex and controversial subject among researchers. Significant brain cell loss is not usually considered an intrinsic part of normal age-related decline. However, it is generally agreed that even healthy people experience some loss of brain cells as they age--particularly after the age of sixty (1). But can exercise perhaps halt or slow down brain cell loss leading to more severe disorders—such as Alzheimer's Disease or other forms of dementia—at least in some individuals? Can exercise have a rehabilitative impact? These questions are particularly relevant when looking at the potential benefits to older adults for improved physical, mental, and cognitive health.

We do know that neuronal loss may occur and can be attributed to genetic predisposition towards Alzheimer's Disease or dementia, but also due to multidimensional factors: including diet, a sedentary lifestyle, or menopause (low estrogen) (1). Increased prevalence of neurodegenerative illness in modern societies has been related to an increasingly aging population (2). A sedentary lifestyle may be a risk factor for neurodegenerative disease, and is associated with a higher risk of cerebrovascular accidents.

Moreover, several studies indicate that exercise may be neuroprotective. In fact, physical activity has been

shown to increase cognitive ability in older adults, attenuate motor deficits, increase new neuron formation, ameliorate neurological impairments, and impede age-related neuronal loss (2).

Cognitive assessments have revealed that regular, moderate-intensity physical exercise enhances mental performance in both young and older adults. Lessons may also be learned in particular from studies of the rat brain, considered very similar biochemically to that of the human. Active or exercised rodents—in comparison to sedentary controls--demonstrate improved spatial learning, enhanced memory retention, reduced escape latency, and diminished age-related declines in spontaneous activity (3).

Increase Of Metabolic Capacity

Studies have shown several structures in the brain that exhibit exercise-related plasticity and which are likely to be active during vigorous physical activity: the hippocampus, motor cortex, and stratum (4). In addition to transient fluctuations in metabolism, studies done on rats and on humans show exercise to cause neurochemical and structural plasticity (ability to respond to stress or demand) in the hippocampus and striatum, the areas of the brain involved in contextual behavior and decision making (4). Again, drawing on rat models, specific metabolic and neural activity can be detected that shows, during exercise, metabolism increases in the hippocampus, striatum, and the motor cortex (4). These studies lend credence to the argument that by stimulating these critical areas of the brain by exercise there are real potential benefits in slowing the progression of neurodegenerative changes in the brain by avoiding being sedentary.

Exercise as Neuroprotective

The effect of exercise on how insulin-like growth factor 1 (IGF-1) impacts brain cells also suggests another positive line of study. Because we customarily produce less IGF-1 as we age, understanding how IGF-1 plays a role in supporting the growth of cells/cellular structures in the adult brain may help in understanding how neurodegenerative diseases such as Alzheimer's or stroke affect the brain. Research in the role played by circulating IGF-1 as a possible neuroprotectant in the brain could reveal that exercise is a buffer against more severe insults on the brain (5), so that that if you do produce more beta amyloid (the abnormal protein that is increased in deposits in people with Alzheimer's), the brain is relatively protected by additional circulating IGF-1.

Exercise is also found to stimulate the up-take of the neurotropic IGF-1 from the bloodstream into such specific targeted areas as the hippocampus. By analyzing the specific role of circulating IGF-1 on brain function under physiological conditions, researchers are trying to understand if physical exercise can result in an increased uptake of circulating IGF-1 by muscles and the brain.

It has also been shown that exercise will increase the number of new neurons in the adult hippocampus. Peripheral administration of IGF-1 results in increases in the number of new neurons in the hippocampal region of hypophysectomized rats (rats without the pituitary gland).

It is speculated that circulating IGF-1 might be facilitating the stimulatory effects of exercise on the number of new hippocampal neurons (in normal adult rats) (4, 5). There is now a general consensus that these new neurons are, in fact, produced on an ongoing basis in the hippocampal dentate gyrus of adult mammals. These new neurons arise from a local population of progenitor or stem cells in the sub granular zone, a specific layer in this section of the brain associated with dramatic cell loss in Parkinson's and Alzheimer's Disease.

Exercise is considered "neuroprotective" because of increased passage of circulating IGF-1 into the brain; when this passage is blocked, exercise is no longer neuroprotective. Additional evidence suggests that systematic administration of IGF-1 to brain damaged sedentary mice or rats is sufficient to elicit functional recovery. Based on these findings, it is hypothesized that circulating IGF-1 exerts a physiological protective effect on the brain—one that is depressed in sedentary subjects. By extrapolating these results in rodents to humans, since studies show that exercise also stimulates the growth hormone-IGF-1 axis in human beings, it is conceivable that a sedentary lifestyle contributes to the increasing prevalence of neurological diseases (2).

Brain Cell Proliferation

In order for exercise to be able to increase the number of new hippocampal neurons, circulating IGF-1 is a necessary factor. Studies show treadmill running, significantly increases the number of replicating neuronal cells (that stain for bromodeoxyurdine in the nuclei) in the hippocampus of adult rats, which also replicates recent findings in mice. Therefore, what is found via exercise, is that Circulating IGF-1 increased the amount of neurons in the hippocampal region of the brain in the group that exercised vs. the group that did not.

Cognitive assessments have revealed that regular, moderate-intensity physical exercise enhances mental performance in both young and older adults.

It can also be speculated that such factors as aging or stress (5) decrease the number of new neurons through up-regulation of endogenous (generated within the body) corticosteroids, and may eventually modulate availability of endogenous neurotropic factors such as IGF-1. When we look at this effect on the aging brain, the positive effect of exercise on the hippocampus (the center of learning and memory) can translate into increased reaction time, thinking, and memory skills.

(continued on page 20)

(continued from page 19)

Brain Injury & Exercise

It has been found that the peripheral administration of IGF-1 has potent therapeutic effects in several models of brain damage; this supports the idea that exercise could indeed have ameliorative effects on more serious insults to the brain, and is supported by evidence that early exercise in concussion or traumatic brain injury may be protective (Traumatic Brain Injury and Mitochondrial Dysfunction JB. Hiebert, Q Shen, AR. Thimmesch, and JD. Pierce, Am J Med Sci 2015;350(2):132–138).

Moreover, it can be extrapolated that IGF-1 could also prove of therapeutic value in hippocampal-related diseases—particularly those involving memory processes—and offers a promising venue for further research. Further support of the idea that exercise improves cognition is shown by the fact that IGF-1 ameliorates memory deficits in aging rats. This is a possible explanation for the beneficial effects of physical exercise on the response to neurodegeneration in diseases such as Alzheimer's, where IGF-1 levels are significantly altered. More research needs to be done in order to determine the potential of exercise to ameliorate brain injury after a stroke (TBI) as the research indicates that memory, thinking, and depression markedly improved among exercisers vs. non-exercisers (6).

The Impact of Sedentarism on Brain Health

Another perspective (7) discusses how circulating IGF-1 facilitates the protective effects of physical exercise against brain insults of different etiology and anatomy. As stated, sedentarism increases the susceptibility to neurodegenerative processes attributable to insufficient brain uptake of serum IGF-1. Several models were used of neurodegeneration affecting different brain areas, because exercise-induced capture of serum IGF-1 is widespread. Since IGF-1 receptors are widely distributed in the brain, neuroprotection by exercise-induced brain uptake of IGF-1 should be ample.

Three models of experimental neurodegeneration affecting different brain areas were utilized to determine whether neuroprotection by exercise includes all types of neuronal populations—or is rather restricted to a few. To test this, three groups of rats were subjected to administration of excitotoxics of various strengths to produce mild, moderate, and severe models of neurodegenerative damage. The purpose was to test both prevention and amelioration of neurodegeneration by exercise.

The results indicated that in all three groups, exercise ameliorated damage-incurred symptoms; many animals recovered substantial function after five weeks of vigorous exercise on the treadmill. When anti-IGF-1 antibody was injected before the exercise, the ameliorative and recovery effects were blocked. Animals receiving the anti-IGF-1 antibody suffered marked neuronal damage similar to that found in sedentary animals.

Thus, exercise was found to not only attenuate the impact of brain insult, but also to impede the progression of ongoing neurodegeneration, as well as functional recovery from insults (7). Exercise reduces or eliminates neuronal death and decreases or entirely blocks behavioral impairment after neurotoxic insult. While knowledge of the mechanisms underlying IGF-1 neuroprotection are scarce -- their possible relation to exercise-induced neuroprotection being unknown--it is speculated that glucose metabolism may be an important factor. Both IGF-1 and exercise may affect glucose metabolism, because energy demands are increased injured neurons. Both IGF-1 and exercise increase demand for available glucose to the brain. In fact, hippocampal damage with domoic acid induces an increase in glucose uptake in the hippocampus (7).

Recent studies indicate that while regular physical activity may be a protective factor against cognitive decline during aging, inactivity, itself, may be a risk factor for dementia. Furthermore, regular physical activity is now recommended as a therapeutic strategy to delay, prevent, or combat neurodegenerative disease (2). However, the molecular mechanisms underlying the advantageous effects of exercise remain unclarified. Specifically, it is somewhat nebulous whether the neurologically favorable sequelae of physical activity extend to neuroprotection.

Oxidative Stress & Antioxidants

Scientists have studied these three questions to understand how relevant oxidative stress and antioxidants are in acute or chronic exercise: 1. Does exercise cause oxidative stress in organs? 2. Does chronic or acute exercise show different effects on oxidative stress in various organs? and 3. What is the relationship between exercise-induced oxidative stress and endogenous antioxidants? The hypothesis is that chronic and acute exercise may have important effects on organs such as the brain, as well as on the muscles and heart and that endogenous antioxidants may play an important role in the adaptation to exercise-induced oxidative stress (10).

Extreme exercise is thought to increase oxidative stress (temporarily) and moderate exercise is thought to increase antioxidant levels. Therefore, depending on the type and duration, it is very well possible that someone's "baseline" ability to fight free radical damage to the brain may be elevated. Considering the aging brain, as well as in the case of neurodegenerative diseases, there is a decline in the normal antioxidant defense mechanisms, which increases the vulnerability of the brain to the deleterious effects of oxidative damage (11). If exercise can "counteract" this effect, there may be important implications for older adults already genetically susceptible to Alzheimer's and related dementias.

Translating the Research

What possible implications do these scientific studies show? What does the impact of exercise on the brain have on potential "at risk" individuals-- those presently suffering from Alzheimer's disease or other types of dementia? Could exercise possibly prevent--or slow down the progression of these conditions? The studies presented confirm that exercise had beneficial effects for those with risk factors for dementia and other types of brain

injury, as the severity of those with the highest level of physical activity was reduced by 50%, along with a 60% decrease in the incidence of Alzheimer's disease (12).

While the studies do not take into account genetic predisposition of Alzheimer's and how that may or may not skew the results, the underlying mechanisms confirm that exercise sustains cerebral blood flow by decreasing blood pressure, lowering lipid levels, inhibiting platelet aggregability, and easing cerebral metabolic demands (12); which implicates that perhaps one genetically at risk may still reap the benefits if they exercise.

As of recently, the benefits of exercise as a preventative measure against more serious neurodegeneration has been studied as a means to prevent, slow down, and/or ameliorate preexisting conditions for the elderly. However, now the overall beneficial effects of exercise on AD (Alzheimer's) has been shown to include lower body weight, improved diet (including increased consumption of antioxidants, and lower fat intake), mood, improved blood pressure and cardiovascular health, and decreased blood clotting (13).

Conclusion

While there is no question that exercise has an overall beneficial effect on the brain--as well as the other areas of one's physiology--exactly how it does so remains a controversial issue. Further areas of research need to include whether or not exercise must be done over a lifetime (cumulative effect) to reap positive rewards, or if one can take up an exercise routine later in life and reap the same positive results. Moreover, the types of exercises health care professionals recommend to their patients need to be appropriate and carefully crafted for seniors with limited mobility and significant health and cognitive limitations.

If Aging Life Care Managers™ and physicians can work together to come up with appropriate exercise plans tailored to the individual's medical and cognitive ability, significant benefits may be realized. Our challenge as care managers is to take into consideration the many different types of exercise, the appropriate duration, consistency, intensity of specific types of exercise appropriate to each individual's current health condition.

While additional research is needed to understand the complexity and non-linearity of the exact mechanisms by which exercise produces an ameliorative effect, it still appears clear that regular physical activity represents a critical and potent protective factor against cognitive decline and dementia in the elderly, paving the way for further emphasis on prevention by including exercise in each care manager's care plan for each of our clients.

References

(1) Schaie, K.W., & Willis, S.L. (1996) Adult Development & Aging. New York: H

(2) Ramsden et al., Exercise increases the vulnerability of rat hippocampal neurons to kainate lesion. Currently in publication.

(3) McCloskey et al., Exercise increases metabolic capacity in the motor cortex and striatum, but not in the hippocampus. Brain Research. 2001; 168-175.

Harper Collins Publishing.

(4) Trejo et al., Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. Journal of Neuroscience. 2001; 1628-1634.

(5) Carro et al., circulating insulin-Like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. Journal of Neuroscience. 2001; 5678-5684.

(6) Williams, GP & Morris, ME. Brain Injury, Aerobic Exercise Following TBI. Brain Injury: Vol 23 (4) April 2009 , pp 307-312.

(7) Berchtold et al., Estrogen and exercise interact to regulate brain-derived neurotropic factor mRNA and protein expression in the hippocampus. European Journal of Neuroscience (2001); 1-14.

(8) Larsen et al., Does long-term exercise counteract age-related Purkinje cell loss? A stereological study of rat cerebellum. Journal of Comparative Neurology (2000); 213-222.

(9) Praag et al., Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nature Neuroscience (1997); 266-270.

(10) Gomez-Pinilla et al., Physical exercise induces FGF-2 and its mRNA in the hippocampus. Brain Research (1997); 1-8.

(11) Liu et al., Chronically and acutely exercised rats: biomarkers of oxidative stress and endogenous antioxidants. Journal of Applied Physiology (2000); 21-

(12) Carmelina Gemma, Jennifer Vila, Adam Bachstetter and Paula Bickford: Brain Aging: Models, methods and mechanisms, Oxidative stress and the aging brain (2007);353-354.

(13) Laurin et al., Physical activity and risk of cognitive impairment and dementia in elderly persons. Archival Neurology (2001); 498-503.

(14) Friedland et al, Patients with Alzheimer's Disease have reduced activities in midlife compared with healthy control-group members. PNAS (2001); 3440-3445.

Footnote

1. White House Conference on Aging National Report: National Institute of Health and Human Services 2015 report

Jennifer E. Voorlas, MSG, CMC

Jennifer E. Voorlas, MSG, CMC has been in the field of gerontology since 1996 when she first participated as an intern in the peer counseling program for seniors, at the Center for Health Aging in Santa Monica CA. While completing her Master's degree in Gerontology in 1998 at The University of Southern California, she worked at the Alzheimer's Disease Research Center at USC, coauthoring a training manual for teachers based upon a pilot program she co-created for at-risk seniors in the community called The Memory Enhancement Seminar for Seniors. As co-administrator of this community outreach program, she was able to learn about the unique needs of a diverse group of elders in the community. Further on in her career she worked within a neurology practice for many years as a sole geriatric care manager/consultant. During this time she also started her own geriatric care management practice in 2011 Geriatric Care Consultants LLC in Malibu, California where she currently resides. She can be reached at geriatriccaring@aol.com.