EXERCISE AND BDNF PRODUCTION AS A FUTURE TREATMENT FOR ALZHEIMER'S DISEASE

by

RUTH ALLAN
TIM COLLINO
HERITAGE OLUWAROUNKE

Pass with Merit

RESEARCH PAPER BASED ON LECTURES AT THE MEDLINK CONFERENCE AT NOTTINGHAM UNIVERSITY IN DECEMBER 2012

17th MARCH 2013
ABSTRACT
This paper is going to explore possible roots for treatment of Alzheimer’s disease, focusing specifically on the role of exercise and its influence on levels of the nerve growth factor, Brain Derived Neurotrophic Factor (BDNF), as an alternative treatment. We will explore various methods that could lead to increased levels of BDNF in the brain, specifically synthesis outside the body and stimulation of BDNF in the brain through drug therapy, as difficulties may arise in the prescription of exercise. This paper will discuss the effects on the brain, impacts on medicine and the ethical implications. This paper concludes that exercise is the most plausible method in reducing Alzheimer’s due to alternative treatments detrimental implications.

INTRODUCTION

Structure of the brain
The human brain is an extremely intricate organ, made of millions of neurons, supported by neuroglia, which collect and transmit electrochemical signals across synapses. Each of these neurons could feasibly be connected to up to 10,000 other neurons in the brain, creating the communication needed for the human body to function. After the first few months following birth no new neurons are created as the existing neurons do not divide. Therefore the neurons in the brain are for a lifetime, hence why damaging them is so detrimental. The structure of the neuron compromises of three main parts: a soma, dendrites and an axon. The soma is the ‘body’ of the cell and contains the nucleus and other organelles such as the Golgi apparatus and mitochondria. Its main purpose is to maintain the cell; however it plays no active role in the transmission of signals. Numerous dendrites are attached to the cell in a branching effect, and it is through these that the inputs enter the cell. Finally the axon of the cell is a long extension whose function is to carry the electrochemical message the length of the neuron.

Communication between neurons is stimulated when an electrical impulse called an action potential travels along the axon of a presynaptic neuron. To cross the synapse the action potential causes the vesicles in the neuron to congregate at the end of the axon (the axon terminal.) The membrane of the vesicles and axon terminal fuse causing the chemicals, called neurotransmitters, inside the vesicles to be released into the synapse. These bind to the receptors on the postsynaptic neuron like a lock and key fit, which in turn creates an action potential on the dendrite of the neuron.

Two of the most common neurotransmitters released into the synapses are glutamate and gamma-aminobutyric (GABA.) Glutamate is the major excitatory neurotransmitter and so stimulates signalling between neurons. The more often an electrical impulse is passed between neurons the more effective glutamate becomes, and since glutamate is eminent in learning, memory and cognitive functions, this is something to be desired. A way in which to make the glutamate more effective is to increase the amount of receptors on the dendrites, which in turn creates a better connection between the neurons, leading to better memory and learning. There is however a dangerous side to glutamate, being that it can be toxic to other nearby nerve cells that are needed for brain cell communication, damaging them irreversibly and causing harm to the person. GABA, on the other hand, is inhibitory and so causes the activities to cease. A balance is needed between the excitatory and inhibitory neurotransmitters for the communication amongst neurons to perform.
**Alzheimer's disease**

Dementia is the term used to describe the deterioration of the mental capabilities of a person; this is split into Parkinson’s disease, Huntington’s chorea and most commonly Alzheimer’s disease, accounting for about two-thirds of the cases of dementia throughout the world. There was an estimated 35.6 million cases of dementia in 2010, a figure expected to double by 2030. Alzheimer’s most commonly affects older people – 10% of people over 65 and an estimated 50% in over 85’s – which could prove to be a growing problem due to our aging population. Symptoms of Alzheimer’s can include short-term memory loss, disorientation, unpredictable mood changes, lack of motivation and trouble with language. Alzheimer’s is a neurological disease resulting in the irreversible loss of neurons. Therefore symptoms vary depending on the extent to which the neurons are damaged. It should also be noted that these symptoms have a significant effect on society, especially the immediate family where the burden of looking after the Alzheimer’s patient often falls. It is estimated that the worldwide cost of looking after dementia patients is $604 billion.

Alzheimer’s disease has no singular cause but can be due to three characteristics resulting in the damage of neurons in the brain as well as enlargements of the ventricles, commonly shown by the reduced size and weight of an Alzheimer’s patient’s brain. One of the characteristics is the reduction in levels of neurotransmitters, such as acetylcholine which combines with the receptor molecule in the postsynaptic neuron, caused by the degeneration of cholinergic neurons (Ugeskr Laeger, 1990). Researchers suggest that the reason for this reduction of neurotransmitters is the loss of cells in the basal forebrain, the part of the brain which produces acetylcholine. Another of the possible causes is the build-up of Neuritic plaques formed as a result of excess Amyloid protein. These are fragments of amyloid precursor protein (APP), being deposited on the brain. These plaques are found in spaces between nerve cells in the brain, although it is presumed they disturb the normal communications between neurons, it is not known precisely how they lead to the symptoms of Alzheimer’s. This is particularly significant in the genetic early onset Alzheimer’s as mutations to gene’s 21, 14 or 1 can lead to increased production of beta-amyloid causing plaque’s to develop. Alternatively, Alzheimer’s can also be as a result of Tau-containing neurofibrillary tangles (Jürgen Götz and Andreas Schild 2004). Tau proteins normally help to stabilize parts of neurons, however with the addition of phosphate groups these can become tangled so the neurons are no longer stable, increasing the likelihood of impairment.

These changes occurring within the brain can be as a result of a number of risk factors, the fundamental one for Alzheimer’s disease being age. This is due to the natural changes that occur in the brain, mainly associated with neurons deterioration and related to the three characteristics previously mentioned. Aside from these, the mitochondrion inside the neurons become more susceptible to damage and therefore the energy required for normal cell functions is not created, which could lead to a further lack of neurotransmitter synthesis. The synapses also undergo degeneration, affecting the rapidity and effectiveness of neurotransmission and therefore causing a decline in the speed and ease in which the mind can recover cognitive functions such as memory. The physical effects on the brain are extensive shrinkage on the cortex which impacts cognitive functions such as memory, decision making and problem solving. The hippocampus, responsible for short term memory, is also significantly reduced.

Another proposed risk factor of Alzheimer’s, similar to heart disease, is high blood pressure. As the works of Shahram Oveisgharan (Feb. 2010.) concludes, control of hypertension could
prevent one-third of patient’s with cognitive impairment progressing to dementia. This may propose a possible link to how exercise may reduce the risk of developing Alzheimer’s disease.

**Effect of exercise on the brain**

It is known that physical activity has an effect on brain and cognition. Sabrina Segal, a lead researcher from UC Irvine’s Center for the Neurobiology of learning and memory, theorizes that an increase in memory skills may be due to a chemical called norepinephrine which is produced during exercise. Previous studies showed that hindering norepinephrine hinders memory while increasing norepinephrine levels can improve memory skills. Therefore even a short session of intense exercise can impact memory skills.

Mitochondria are the cell organelles in which respiration takes place, supplying our body with energy. It is known that during exercise muscle cells produce new mitochondria to fulfil the energy demands of exercise. J. Mark Davis, a physiologist at the University of South Carolina has asked if brain cells responded the same way during exercise. While studying the effect of exercise on mice, the increase in the signalling molecule for mitochondria production was evident. The increase of energy supply allows the brain to work faster and more efficiently – improving cognitive functions. This could help in understanding how exercise starves off age-related declines in brain function “because neurons naturally lose mitochondria as we age”, Davis explains. He goes on to say that “the evidence is accumulating rapidly that exercise keeps the brain younger”. Exercise also increases the density and size of the brain capillaries, which increases the blood flow and supply of oxygen to the brain.

Although it is known that exercise improves brain health and cognition, how it does this is unknown. Carl Cotman, a neurobiologist at the University of California, Irvine, believes that the key is a group of chemicals called Nerve growth factors which play a vital role in nourishing the nerve cells and promoting cell health. A growth factor called Brain-derived neurotrophic factor (BDNF) mediates the creation of more receptors and neuron in the brain which is said to improve brain function as it helps support the survival of new neuron. This is useful since neurons get damaged irreversibly in dementia patients. Studies show that the level of BDNF increases in the brains of animals that run and people that exercise and there is a direct relationship between the amount of exercise and the level of BDNF. After exercise levels of BDNF are elevated in motor areas of the brain but also areas associated with learning and memory. Therefore increased BDNF is associated with more effective memory and better learning, which would be helpful for dementia patients. It has also been linked to lowering levels of depression and anxiety and an overall improvement of the emotional health of patients.

**DISCUSSION**

BDNF could be the answer in preventing or reversing Alzheimer’s induced brain deterioration. Some other effects of Alzheimer’s disease are also the degeneration of function in neurons which BDNF is known to prevent as it keeps neurons alive and healthy. The effects of this growth factor shows early promise for halting and reversing brain-degeneration diseases like Alzheimer’s disease as research that has been carried out shows that animals injected with BDNF or given the gene that produces BDNF showed less problems with cognitive functions. The study by researchers at the University of California, San Diego show early promise that BDNF as a treatment could potentially slow down or starve off Alzheimer’s disease. “The effects were potent,” said Mark Tuszynski, MD, PhD, lead researchers. “When we
administered BDNF to memory circuits in the brain, we directly stimulated their activity and prevented cell death from the underlying disease.” As a result of BDNF in the brain, brain cells that should have died because of Alzheimer’s did not, and brain cells that had degenerated were revived. This provides evidence that BDNF could be the future in ‘curing’ Alzheimer’s disease.

BDNF treatment could be used as prevention as it “targets the cortical cells themselves, preventing their death, stimulating their function, and improving learning and memory” said Dr. Tuszynski. Encouraging young people to take part in regular exercise more should stimulate increased BDNF production and reduce the ‘aging effect’ on the brain in order to reduce the risk of Alzheimer’s. BDNF could be seen as a “fountain of youth” for the brain. The deterioration of the brain as a result of Alzheimer’s disease could potentially also be slowed down or the progression of the disease could be stopped by BDNF treatment. The hippocampus is one of the first regions of the brain that suffers pathological damage as a result of Alzheimer’s disease. Notably, brain cells in the hippocampus become larger and show stronger connections after experimental animals were given BDNF. Although the protective and restorative effects of BDNF has no effect on the build-up of beta-amyloid in the brain that forms the plaques of Alzheimer’s disease, many current experimental treatments targets inhibiting beta-amyloid production. There is a potential to combine BDNF and amyloid-based treatments which Dr. Tuszynski said will theoretically provide a two-pronged attack on the disease.

Since it is known that exercise stimulates the production of BDNF, it must be acknowledged that the first step to solving the problem of Alzheimer’s may be exercise at a younger age. Therefore one method could be increasing funding in schools for equipment in order to boost levels of participation, along with involving exercise in compulsory subjects such as physical education at school, and to encourage exercise in the work place. Government funding could also be directed extra-curricular clubs and activities, which in turn would increase participation levels in both children and adults. Furthermore, it could also have a positive effect on other increasingly prominent health issues such as; obesity, heart disease and general health of the population.

One possible difficulty for a doctor in prescribing exercise as a treatment for an individual may be simply the lack of reliability of a patient to see it through. This could be due to whether or not the patient takes the prescription due to the increasingly more common expectation of receiving a form of drug or medication from a doctor, and therefore feel that exercise itself is insufficient. As well as this patients may be inclined to refrain from exercise due to a lack of time within their normal daily routine. Alternatively patients may struggle to perform exercise due to a lack of motivation.

Another difficulty when proscribing exercise is variation of physical conditions from patient to patient. Patients could have other chronic illnesses such as Asthma, which depending on the severity of the condition could have a substantial effect on their ability to carry out exercise; therefore this should be taken into account when deciding on both intensity and duration of an exercise program. This in turn could have a negative effect on the likelihood of a patient to complete the proscribed exercise due to implications it may have on their illness. As Alzheimer’s patients are more likely to be elderly and potentially frail their ability to partake in exercise may be hindered. Exercise programs could be designed in order to be less strenuous. However lack of effective exercise and injury are more likely in the older patient. Alzheimer’s may further initiate difficulties as in its late stages it can cause progressive muscle
weaknesses in the arms and legs (Jun Y Cho 2003). So caution should be exercised when prescribing exercise as a treatment for Alzheimer’s. Therefore other ways of producing BDNF is better for the treatment of Alzheimer’s.

If BDNF could be produced outside the body, similar to how stem cells are cultured, and then it could be introduced into the brain. If the gene that produces the protein BDNF could be located and placed into the plasmid of a fast reproducing bacterium, or already existing BDNF could be replicated, then this externally manufactured BDNF could be inserted into the brain. This would increase the patient’s chance of attaining control of their cognitive functions and so lead to a better quality of life.

The BDNF could not be taken orally since the digestive enzyme protease would hydrolyse the protein, making it ineffective. Also subcutaneous injection of BDNF would be futile since the blood brain barrier would restrict the passage of large protein molecules including BDNF.

There is however an alternative entrance into the brain, which would involve injecting BDNF into the cerebral spinal fluid, via a lumbar puncture. This may be effective but is susceptible to infection, therefore requiring sterile hospital conditions. The procedure is already performed in obstetrics and the technique could be adapted for treatment.

Only specific regions of the brain, such as the hippocampus, need extra BDNF and if the whole brain is flooded with excess BDNF it could be damaging, resulting in seizures due to the increased neuron excitability. For this experimental technique to be beneficial, a method is required to locate areas deficient in BDNF, meaning synthetic BDNF is only released to depleted regions.

A possibility would be to encapsulate the BDNF in a material which can recognise certain areas of the brain, depositing the protein where necessary. Nanotechnology could be a potentiality in the future since nanoparticles are currently being developed to deliver chemotherapy drugs directly to the cancerous cells without damaging any of the healthy cells. Therefore if research continues in this field then nanoparticles could feasibly be used to treat Alzheimer’s patients. There are concerns over nanoparticles causing lung damage; therefore further research is required into this methodology before considering human trails.

Another possibility is synthetically producing BDNF via a recombinant DNA process, similar to synthesising insulin. In this approach the BDNF producing gene could be placed into the plasmid of a fast reproducing bacterium such as Escherichia coli or yeast, this would result in rapid synthesis of harvestable BDNF.

BDNF production could be stimulated by a drug enhancing the benefits of BDNF, as previously described, without having to do exercise. Drug inducers could potentially be more beneficial than synthetically produced BDNF as it would allow the BDNF to be produced more naturally. If a drug could stimulate its’ production then positive effects would probably be seen with increased cognitive function. Issues would arise in firstly finding a drug that could increase the levels of BDNF but also that doesn’t affect any other neurons or chemicals in the brain. A clinical trial published in the ‘Journal of Alzheimer’s Disease’ showed that lithium could induce BDNF and therefore have a positive impact on the diminishing of cognitive impairments. Further research with this drug could be beneficial. Drug related research would need to produce a dose response curve calibrated to different stages of Alzheimer’s disease.

These treatments of synthetically produced BDNF have many ethical implications which would need to be addressed accordingly. One ethical dilemma is that by producing drugs
as an alternative to exercise people may feel it is unnecessary to be active since the drug can work just as well for prevention of Alzheimer’s. There are many other positive effects of exercise, such as cardiovascular protection and a lower blood pressure. Introducing a drug could lead to an increase in obesity and myocardial infarctions; something the NHS already spends £4.2 billion on a year.

Clinical trials are an important part of the future of BDNF on Alzheimer’s before the BDNF treatment can be tested on humans, they have to undergo extensive investigation in order to be considered safe. However, the long-time side effects of synthetically produced BDNF being injected into the cerebral spinal fluid are currently unknown. Extensive animal testing will be required. Although BDNF is a natural protein more research would be required into whether it has to be naturally produced by the brain in order to avoid any side effects. Research into the effect of BDNF on the mouse’s brain is currently taking place but the side effects on animals could be different to humans. Animal testing is also seen as unethical by a section of the population. If the treatment is considered safe according to the standards set by the European Union Clinical Trials Directive, testing on healthy human volunteers can then take place in Phase I. Introducing BDNF via a lumbar puncture may have issues; BDNF has a relatively short half-life so frequent injections may have an adverse impact on a patient’s quality of life.

CONCLUSION

There are no current treatments to cure Alzheimer’s however drugs such as memantine and donepezil are being used to help with symptoms. However in this paper it has been suggested that a prescription of exercise could be a way to prevent or reduce the effects of Alzheimer’s Disease, although the complications of this method of prevention have also been discussed, namely the unreliability and uncertainty on the patients behalf. This led us to explore alternate ways to increase BDNF levels in the brain.

In this paper we have considered the artificial production of BDNF and stimulating production via drug inducers. These techniques, whilst untested and only hypothetical, seem to have many positives including rapid addition of BDNF, reliability of treatment and accessibility for those who struggle to exercise. Conversely there are many complexities such as obtaining entrance into the brain, due to digestive enzymes and the blood brain barrier. We concluded that a lumbar puncture would be the best method for transmitting synthetically produced BDNF. However since the majority of the patients would be elderly, this procedure could potentially be more detrimental than beneficial. Therefore its use would need to be considered depending on the needs of the individual. Other areas of concern were avoiding flooding the brain with BDNF and instead introduce it to specific regions. A possibility could be to use nanotechnology to locate the areas where BDNF is needed. This would be unrealistic now but with advances in nanotechnology, such as in fields like cancer research, it could be a genuine possibility for medicine in the future. Drug inducers could be seen as more desirable since the drugs could be taken at home, hence overcoming the problem proposed in synthetically produced BDNF whereby the patient would need frequent hospital visits. Furthermore the discomfort of the patient would be reduced since lumbar punctures would not be required. Consequently, improvement to the patient’s quality of life would be attained. Therefore drug inducers would be preferable to externally produced BDNF however the latter seems a more realistic option in the future.
Overall our conclusion is that exercise is the more favourable option since the BDNF is naturally occurring so there no side effects, unlike artificial alternatives. Additionally exercise can have positive effects on the body as well as the brain reducing other health risks. Therefore exercise is the future of medicine in the diminishing of Alzheimer’s disease.

REFERENCES


http://www.tandfonline.com/doi/abs/10.1080/0264041031000140365

http://www.human-memory.net/brain_neurons.html

Paul A. Adlard, Victoria M. Perreau (2005) Voluntary Exercise Decreases Amyloid Load in a Transgenic Model of Alzheimer's Disease
http://www.jneurosci.org/content/25/17/4217.short


Sabrina Segal, Carl Cotman, and Lawrence Cahill
UC Irvine Center for the Neurobiology of Learning and Memory

Amyloid-induced neurofibrillary tangle formation in Alzheimer's disease: insight from transgenic mouse and tissue-culture models (Jürgen Götz, Andreas Schild, Fred Hoerndli, Luis Pennanen)

Alzheimer’s society website

Brain Factor BDNF Shows Early Promise Against Alzheimer's – by Alzheimer's Information site - reviewed by William J. Nietzer (13th April 2009)
http://www.alzinfo.org/04/articles/prevention-and-wellness-23

BDNF Prevents and Reverses Alzheimer's disease by Byron J. Richards (11th Feb 2009)
http://www.wellnessresources.com/health/articles/bdnf_prevents_and_reverses_alzheimers_disease/
Brain Plasticity and behaviour (Bryan Kolb and Ian Q. Whishaw, 1998)
http://www.annualreviews.org/doi/abs/10.1146/annurev.psych.49.1.43

Exercise: a behavioral intervention to enhance brain health and plasticity
(Carl W. Cotman, Nicole C. Berchtold, 2002)

Exercise and Cognitive Health reported by Dan Peterson (25th July 2011)

Health Risks Of Nanotechnology: How Nanoparticles Can Cause Lung Damage, And How The Damage Can Be Blocked. report by ScienceDaily. (June 11, 2009)

How Exercise Jogs the Brain, reported by Stephani Sutherland (16th February 2012)
http://www.readcube.com/articles/10.1038/scientificamericanmind0312-12a

How Human Memory Works, report by Richard C. Mohs, PhD.

Move Your Feet, Grow New Neurons? report by Brenda Patoine (1st May 2007)

Nanotechnology in medicine, reported by understandingnano
http://www.understandingnano.com/medicine.html

National Institute on Aging
http://www.nia.nih.gov/alzheimers/topics/treatment#drugs

Neurotransmitters in Alzheimer's disease (Ugeskr Laeger. 1990 Jul 23)

Prescribing exercise for frail elders. (John M Heath and Marian R Stuart, 2002)
http://www.jabfm.org/content/15/3/218.short