How exercise affects BDNF and possible applications of this in the future treatment of Alzheimer’s

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Pass with Merit

Research Paper based on lectures at the Medlink Conference at Nottingham University in December 2012

Date here:
March 2013
ABSTRACT

With studies linking BDNF to improvements in diseases such as Alzheimer’s, depression and other degenerative and mood related diseases, the use of BDNF in upcoming medicine and drug development is almost inevitable. This paper will focus on the use of BDNF in conjunction with the treatment of Alzheimer’s. By increasing levels of BDNF in areas such as the hippocampus, where the brain is most affected by Alzheimer’s, neurogenesis, synaptogenesis, neuroplasticity, mitochondrial growth and the survival and differentiation of developing neurons can be increased. Factors, all of which have the potential to reduce the symptoms of Alzheimer’s. Ideas for possible treatments such as the use of exogenous BDNF administered by injection, prescribed exercise, diet and the possible development of a drug to selectively inhibit the reuptake of BDNF have been explored. Issues of the blood brain barrier and reduced bdnf signaling due to brain inflammation have also been addressed.

INTRODUCTION

BDNF or brain derived neurotropic factor is a neurotransmitter included in the nerve growth factor family. Recent scientific developments, have led to a growing interest in this particular neurotransmitter in conjunction with learning and brain development. BDNF has neuroprotective effects, meaning it can result in a reduction to brain injury and the delay of the onset of decline in several neurodegenerative diseases (Cotman C, 2007). BDNF has been proven to promote neurogenesis; the growth and differentiation of new neurons in areas of the brain where BDNF is active. It has also been shown to promote synaptogenesis by increasing the number of dendrites and receptor sites at the postsynaptic cells. Increases in dendritic length, dendritic complexity, spine density and neural progenitor proliferation are also known effects of BDNF mediated synaptogenesis. Mitochondrial growth in the brain is another positive effect mediated by BDNF. Possibly the most important breakthrough in this field of neuroscience is the proof of the hypothesis that cardiovascular exercise increases levels of BDNF synthesised by the brain and nervous tissues. It has been shown that physical activity leads to a calcium influx, which activates transcription factors in existing hippocampal neurons. These transcription factors indicate expression of the BDNF gene, which leads to the synthesis of new BDNF proteins. The gene expression is increased in hippocampal neurons in response to exercise; this occurs several days after the initial exercise begins. In parallel with the effects of exercise on hippocampal cytoarchitecture and electrophysiological properties, exercise increases the levels of synaptic proteins (synapsin and synaptophysin), glutamate receptors (NR2b and GluR5) and the availability of several classes of growth factor including BDNF and insulin-like growth factor-1 (IGF-1), which can enhance plasticity.

The stimulation of BDNF production by exercise has been shown to be highest in areas of the brain such as the hippocampus, cortex and basal forebrain. These areas of the brain are parts of the limbic system, which govern all emotional aspects of behavior. They are also the areas of the brain most affected by dementias such as Alzheimer’s disease. It is due to this intriguing fact that may researchers have become interested in BDNF as a possible treatment and even perhaps cure for diseases such as Alzheimer’s, depression and other degenerative and mood related diseases.

It is thought that one way to relieve and improve the symptoms of these diseases is to raise the levels of BDNF in the effected area/s of the brain. As we have seen levels of BDNF are raised
by exercise, could exercise then be used as a possible treatment for these many neurological diseases?

Exercise has a profound effect on the brain’s biochemistry. Exercise regulates learning, neurogenesis and angiogenesis through growth factor cascades. BDNF appears, from current research to be the growth factor with the greatest potential in disease treatment. In animal studies, exercise increases BDNF in several brain regions, and the most robust and enduring response occurs in the hippocampus. During tests on humans taking part in voluntary exercise, an increase in the expression of BDNF and its receptor, synapsin 1 (mRNA and phosphorylated protein), growth-associated protein (GAP-43) mRNA, and cyclic AMP response element-binding (CREB) mRNA were also recorded (Gómez-Pinilla F, 2002). This highlights the strong link between exercise and the expression, and synthesis of BDNF in humans. It also clarifies, that as the levels of BDNF are increased, as are the elements required to synthesise new neurons. Receptor sites are also shown to increase, this means that with increased exercise, pathways regulated by and dependent on BDNF will function on a higher level. Participation in physical activity delays onset of and reduces risk of Alzheimer disease, Huntington’s disease and Parkinson’s disease, and can even slow the decline of brain function after neurodegeneration has begun. The proof that exercise mediated BDNF production in humans is key, we are now able to conclude that BDNF can in some way be utilized in the treatment of degenerative diseases in humans.

An increase in all of the positive factors provided by BDNF will inevitably increase the memory and learning ability of the certain individual. This is due to the fact that high levels of BDNF in the brain lead to the forging of new synaptic pathways (synaptogenesis), neurogenesis in areas of the mid brain such as the hippocampus, cortex and basal forebrain, the increase in receptor sites and mitochondrial growth. All of which are key components to learning and memory. There are many studies clearly showing a correlation between amount of cardiovascular exercise undertaken and increasing levels of free circulating BDNF. Due to the beneficial effects of what many have called the “wonder molecule”, the use of BDNF in the future of medicine and drug development is almost inevitable.
DISCUSSION

During the course of this paper I will explore the possibilities of using BDNF in the treatment of dementia. I will focus mainly on the effect of BDNF on Alzheimer’s patients. Alzheimer’s disease is one of the most common causes of dementia and is a protein mis-folding disease. Transmembrane protein amyloid precursor protein, thought to be involved in neural development, gives rise to the abnormal bi-product amyloid β. After its release, the structure of the abnormally folded amyloid β protein changes, causing the production of amyloid fibrils. These fibrils deposit out side of neurons forming neuritic and amyloid plaques, and also inside blood vessel causing congophilic angiopathy. Alzheimer’s disease is also considered to be a tauopathy, this is due to abnormal aggression of the tau protein. In Alzheimer’s disease, hyperphosphorylated tau accumulates in the nerve cell bodies forming neurofibrillary tangles.

In patients suffering with Alzheimer’s, glutamate is produced in excessive amounts causing destruction and death to the already damaged neurons. Memantine; a drug used to block glutamate, is prescribed by GPs to dementia patients suffering from Alzheimer’s. This drug lowers the levels of the glutamate neurotransmitter in the brain, saving neural cells from further damage. Despite the benefit of saving neurons provided by this drug there is a downside. Lower levels of glutamate in the brain lead to far less efficient messaging between neurons. Glutamate is an excitatory neurotransmitter that increases the permeability of the postsynaptic membrane to cations. This causes Na+ ions previously located in the synaptic cleft to diffuse into the postsynaptic neuron. The neuron is then depolarised locally by the influx of Na+, this depolarisation is the way impulses are carried along the neuron. Therefore a drug reducing the levels of glutamate in the brain would surly lead to reduced learning efficiency and memory. By prescribing BDNF to the patient along side these drugs the remaining glutamates effectiveness can be greatly increased, providing the patient with improved memory and cognitive function. The creation of these receptors is mediated by BDNF, which is why there number increase after the levels of BDNF have been raised by exercise.

The drugs donepezil, rivastigmine and galantamine are also prescribed. Alzheimer’s sufferers continuously lose neurons that use acetylcholine as a chemical messenger. These drugs act as non-competitive inhibitors binding to an allosteric site of the acetyl cholinesterase changing the shape of its active site, and thereby preventing the break down of acetylcholine. Increasing the levels of acetylcholine, leads to increased communication between nerve cells using acetylcholine as a chemical messenger. Increased communicating between nerve cells is the key to memory and learning, both of which are deteriorating in Alzheimer’s patients.

BDNF also mediates the activity of the alpha-7 nicotinic receptor, a cholinergic receptor that forms the ligand-gated ion channels in the plasma membranes of certain neurons, and on the post synapic side of the neurotransmitter junction. If we could use BDNF in such a way that we could control these nicotinic acetylcholine receptors, then the increased communication between nerve cells would create an improvement in the symptoms of Alzheimer’s disease. I am well aware that the drugs donepezil, rivastigmine and galantamine are effectively doing the same thing by preventing the breakdown of acetylcholine, but I believe that if the two were use in conjunction with each other, communication between neurons using acetylcholine as a neurotransmitter would be greatly improved. This increased signaling across the synapses of the neurons mentioned, would dramatically increase learning, memory and cognitive ability, all of which are severely affected by Alzheimer’s disease.
Expression of the BDNF gene is reduced in Alzheimer's patients, so they have reduced ability to synthesise the BDNF protein and can not reap its positive effects. This results in a greatly reduced ability to perform neurogenesis, or any other functions mediated by BDNF. As a result the only way to improve symptoms would be to administer exogenous BDNF via injection. Theoretically it would be possible for BDNF to be manufactured exogenously using genetic engineering. Endonucleases would be used to recognise the BDNF base sequence along the DNA molecule, and cut the DNA at the start and end of the BDNF base code. The BDNF gene would then be released and removed from the donor cell. The bacterium *Escherichia coli* would most likely be used as the host cell. This is due to its prokaryotic nature. As it has no true nucleus only plasmids containing genetic information it is relatively easy to manipulate its genetic code. The plasmid of the *E.coli* bacterium would be removed and cut open using a restriction endonuclease. The BDNF gene would then placed inside the open plasmid using DNA ligase. The recombinant plasmid would then be placed with host bacterium, and the bacterium provided with ideal conditions to grow and proliferate inside a bioreactor. The *E.coli* would then begin to synthesis BDNF, which could then be extracted and used in the treatment of patients. I am unaware of whether this process has been tried and tested with the BDNF gene, but I see no reason why it should not be successful. The only possible limitation would be the ethical issues behind genetic engineering.

The exogenous BDNF, once ready would have to be adminstered to patients via injection to avoid digestion of the protein that would occur if the BDNF was prescribed in capsule form. Here we meet the problem of the blood brain barrier. Despite its usual beneficial role in preventing toxic substances from entering the brain, the blood brain barrier poses a great difficulty in the treatment of the brain through the body. This is due to the fact it creates an impermeable lining to the blood vessels in and surrounding the brain. Normally neurotropic factors are unable to pass through. However, due to the research of Zhang Y and Pardridge WM, we are able to see that BDNF is capable of passing through the blood brain barrier when it is artificially bound to another protein that is capable of passing through the barrier. One approach to the blood brain barrier problem is to attach the nontransportable peptide to a brain targeting vector, which is a peptide or peptidomimetic monoclonal antibody (MAb), that is transported into brain from blood via an endogenous blood brain barrier transport system (Zhang Y, Pardridge WM, 2001). This fact opens up many possibilities in the treatment of the brain using BDNF. If this theory could be successfully carried out and the recombinant BDNF administered to Alzheimer’s patients, dramatic improvements in symptoms would hopefully be seen. One of the main difficulties in treating Alzheimer’s with any growth factor in this case BDNF, is the fact that mechanisms such as brain inflammation interfere with growth factor signaling. In Alzheimer’s patients brain inflammation is a hugely common symptom. The way this must be tackled is through exercise. The inflammation mechanism is modulated by exercise in the periphery and in the central nervous system. By prescribing exercise along with any other drug or supplement that directly or indirectly leads to raised levels of BDNF, we can increase BDNF signaling and so create a far more effective treatment.
In humans, effects of exercise have been clearly demonstrated in aging populations. Sustained exercise participation has been shown to enhance learning and memory, improve executive function, counteracts age-related and disease related mental decline, and protects against age-related atrophy in brain areas crucial for higher cognitive processes. Intervention studies demonstrate that individuals with Alzheimer's who exercise show improved function on the daily living scale, slowed rate of decline in cognitive tests, improved physical function and decreased depressive symptoms, as compared with non-exercisers who show continued decline. As explained earlier, Alzheimer’s patients develop neuritic and amyloid plaques due to the build up of insoluble amyloid-β. Exercise can provide a benefit here too. In mouse models, exercise reduces the load of amyloid-β plaques in the hippocampus and cortex, possibly by regulating processing of the amyloid precursor protein and/or increasing degradation and clearance of amyloid-β. Importantly, exercising animals show improved hippocampus dependent learning. This is proof in its self that all Alzheimer’s treatment should be supplemented with a prescribed exercise schedule.

BDNF stands out for its hugely important ability to regulate synaptic plasticity and various cognitive functions of the brain. Impaired hippocampal synaptic function is one of the many symptoms of Alzheimer’s disease. This too shows the benefits exercise would provide for Alzheimer’s sufferers. With BDNF levels being raised by exercise and BDNF increasing synaptic plasticity and inducing neurogenesis, it is possible that instead of providing exogenous BDNF to Alzheimer’s patients via injection, GP’s could simply prescribe a daily exercise schedule to those suffering from the disease. Exercise has a profound positive effect on the brain, as explained earlier by Cotman C. Studies in humans have shown that the type of exercise undertaken by the patients does not have to be particularly strenuous. Light exercise leads to the same stimulus of BDNF production as more rigorous exercise. It is possible that light exercise may even be more beneficial. Strenuous exercise posses a large stress on the body, leading to the release of stress hormone such as cortisol. The stress hormones have a negative effect on the brain especially the hippocampus. Excess amounts of cortisol produced under stress can impair the hippocampus by preventing one from being able to form a new memory and retrieving an existing memory. These stress hormones are also hindering the hippocampus from receiving enough energy, by diverting glucose levels to surrounding muscles. The production of these hormones effectively cancels out the good that is done by the increased secretion of BDNF. The idea that light exercise may be more beneficial to the body is a bonus. It makes prescribed exercise more appealing for the masses and also allows the more senile sufferers of Alzheimer’s, who may not have been physically capable of rigorous exercise, to reap the benefits provided by BDNF and other exercise dependent mechanisms.

Diet could also be a factor used to raise levels of BDNF in Alzheimer’s patients. Studies show effects of exercise on the brain can be enhanced by concurrent consumption of natural products such as omega fatty acids or plant polyphenols (van Praag H 2009).
Some foods such as those high in resveratrol (dark fruits) have been proven to raise levels of BDNF in the human brain. Iceberg lettuce is high in acetylcholine, as mentioned earlier donepezil, rivastigmine and galantamine are raising the levels of acetylcholine by preventing its breakdown. By eating a diet high in choline rich foods, more free circulating acetylcholine is available for increased communication between nerve cells using acetylcholine as a chemical messenger. This natural way of raising levels of BDNF, could be used in those patients who experience bad side effects from drugs such as donepezil, rivastigmine and galantamine. This method may not produce the same high levels of BDNF but may still be significant enough to make a difference. Perhaps in those who are unable to exercise for various reasons, if diet and exogenous BDNF infections were prescribed together the effects would be more beneficial to the patient than if a single method was used.

There are still many areas around BDNF and its pathways through the brain that are unclear. I am unsure from research whether it is free circulating BDNF, BDNF bound to receptor sites or BDNF in presynaptic vesicles that contributes to its many positive effects on the brain. Possibly it could be all three acting together. If we took the view that free circulating BDNF was the main contributor to neurogenesis, synaptogenesis and its many other effects, in theory we could use this to our advantage when treating Alzheimer’s. In the same way as we use selective serotonin reuptake inhibitors, we could externally modulate the levels of free circulating BDNF in the brain. By designing a drug to selectively inhibit the re-uptake BDNF we would most certainly create an increased level of free circulating BDNF in the brain, and the positive effects would play a huge role in the relief of the symptoms of Alzheimer’s. On the other hand, however this may cause huge knock on effects in the brain and nervous system due to levels of neurotransmitters being unbalanced. Due to the sensitive nature of the brain and our limited understanding, inhibiting the reuptake of BDNF may cause a shortage of the neurotransmitter in the presynaptic vesicles; this would either lead to a greater rate of natural synthesis of BDNF or a shortage. If the latter was the case, the treatment would have to be administered along side a treatment that would rise the synthesise of BDNF in the affected areas, for example prescribed exercise. Extensive animal trials would have to be carried out to create a safe and reliable drug. This then raises ethical issues on the subject of animal testing. If this idea was to prove correct and a drug could be successfully designed, perhaps the effect on Alzheimer’s treatment and in fact the treatment of many other neurological conditions would be so improved this would out weigh any ethical issues?
CONCLUSION

In conclusion the use of prescribed exercise in the treatment of Alzheimer’s is almost inevitable. In all areas of possible treatment I have considered, the use of exercise in conjunction to the treatment is too beneficial to not be utilised. With the increase in levels of exercise, the brain’s availability of several classes of growth factors also increases. These growth factors modulate nearly all of the positive functions enhanced by exercise. This fact sums up the reason why exercise is so beneficial to the brain, and how beneficial it could be in treatment of Alzheimers. By raising the levels of BDNF in patients suffering from Alzheimer’s, an improvement in symptoms could be seen. The increased levels of BDNF would provide greater levels of, survival and differentiation of neurons, mitochondrial growth, synaptogenesis, neurogenesis and synaptic plasticity. Alzheimer’s patients show a decreased level in all these factors including the expression of the BDNF gene, this leads to the degeneration of the brain so often seen in Alzheimer’s. Therefore by raising levels of BDNF, an improvement in symptoms should be seen. For those patients who have severely reduced BDNF expression it may be possible for exogenous BDNF to be administered as a supplement via injection, to help raise the reduced levels in the brain. Possibly a more cost effective way of producing the same effect, would be the development of a drug to selectively inhibit the reuptake of BDNF. However the effects of altering levels of BDNF beyond there natural levels in the brain, may have many unknown side effects. BDNF, if not used responsibly, may also be seen as unethical, as it could potentially be engineered to artificially raise levels of intelligence. The benefits of BDNFs use however, far out way any negative aspects. If GPs used methods previously mentioned to raise BDNF levels along side normal dementia drugs, prescribed exercise and an improved diet, Alzheimer’s symptoms could be reduced significantly. With scientific knowledge developing, it is possible a cure for degenerative diseases may be found via improved knowledge of the workings and pathways of BDNF.
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