A Summary Article of the Role of BDNF

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ABSTRACT
Brain-derived neurotrophic factor (BDNF) plays a role in memory formation, synaptic plasticity and function, synapse formation, synaptic efficacy and neuronal connectivity. It is thought that BDNF production is correlated to both environmental and developmental factors, hence according to studies, increased production of the BDNF hormone reveals an increase in neurogenesis, neurite growth, electrocognitive activity and other processes involved in the use of the hippocampus which show an enhanced activity. It has been reported that exercise helps increase the levels of BDNF, which in turn, improves cognitive function in both humans and rodents. The present paper examines the nature and function of BDNF in the hippocampal formation and how changes in the expression of this protein affect both mind and body. Increased concentrations of BDNF in the brain reflect further benefits of the mind, including enhanced learning ability and memory improvement. Exercise greatly increases BDNF levels in the hippocampus region, and from experimental research, we can judge that the use of exercise to release BDNF can help us avoid depression and Alzheimer’s disease.

INTRODUCTION
Neurotrophins, such as that of NGF (nerve growth factor), BDNF (brain-derived neurotrophic factor), NT-3 (neurotrophin 3) and NT-4 (neurotrophin 4) are produced in sympathetic and sensory target organs and target tissues in the brain, to support neuronal formation and survival. Neurotrophins promote the stabilization of cellular components, which are responsible for neurotransmitter release, leading to an increase in the number of functional synapses, which are vital to brain development. During development, neurotrophins stimulate and guide neuron differentiation in the central nervous system, in addition to the protection of existing neurons and the provocation of synapse formation. Electrical signals cause the release of chemical neurotransmitters which then cross the synapse and stimulate the post-synaptic receptors. Neurotransmitters fit onto the receptor sits on the dendrites which open ion channels in order to change chemical signals into electrical signals in the brain. The protection and formation of such neurons are important in the acquisition of new skills, as well as for thought processes and brain function.

Brain-derived neurotrophic factor, also known as BDNF is encoded by the gene BDNF. In the brain, BDNF is released by a nerve cell or a support cell, such as an astrocyte, which then binds to a receptor site on a nerve cell. This causes a signal to be produced, which is sent to the nucleus of a receiving nerve cell. In this nerve cell, it stimulates the release of the BDNF protein. This particular protein exists as part of the neurotrophic network, such as that of neurotrophin-3 and neurotrophin-4, which direct growth and differentiation of neurons in the developing nervous system. BDNF regulates the transmission of synapses and activity-dependant plasticity, and aids in the survival of neurons.

BDNF is a growth factor for nerves and supports the survival of existing neurons, as well as aiding in the stimulation of stem cells to make new cells and new connections. Both nerve-transmitting cells and glial cells in the brain secrete the protein, BDNF. New studies in rodents suggest that BDNF is needed for the repair of damaged networks in the hippocampus. Stress is thought to lower the amount of BDNF produced, while exercise increases BDNF levels. Avoiding stress and retaining a positive mood is related to maintaining a healthy supply of BDNF. Studies, (Tsai) show that pantethine may be an ideal nutrient to help support BDNF production.
BDNF expression is lowest in both humans and animals at birth and increases up until adulthood. Research into rat development has illustrated that BDNF, along with other proteins such as NT-3 and NGF mRNA increased rapidly during embryonic days 11 and 12, and levels were completely distributed by day 13. These results show a positive correlation with neurogenesis in the peripheral and central nervous system in humans, especially in certain hippocampal neurons. Studies of mice lacking BDNF demonstrate how the production of this neurotrophin is essential for a healthy physical and psychological development. It has been demonstrated through scientific studies, such as that of Mercader, of both humans and rodents that low levels of BDNF in the brain are associated with a variety of neurological impairments such as depression, schizophrenia, obsessive-compulsive disorder, Huntington's disease and anorexia.

DISCUSSION

How does exercise affect BDNF?

Numerous studies (Gomez-Pinilla, 2003) examining the effects of BDNF have shown that physical activity can help in maintaining and preventing the deterioration of nerve cells. Exercise leads to the release of BDNF and other neurotransmitters. The effect of exercise to stimulate BDNF production relies on the activation of a cAMP-response-element binding protein, as it has been found that blocking the use of this protein during exercise suppresses the release of BDNF. Exercise leads to better defined cell-signalling pathways associated with neurogenesis, neuronal survival and improved hippocampal function. Exercise also leads to beneficial effects within the brain, as it stimulates the production of nerve-protecting compounds, increased blood flow to the brain, decreased risk of heart and blood vessel diseases. It does this by altering the damaged proteins in the brain, which is thought to slow the development of Alzheimer's disease. It is considered that the mild stress experienced during exercise stimulates a calcium reflux in the brain, which may then activate transcription factors in existing neurons in the brain. These transcription factors initiate the release of BDNF, creating BDNF proteins which aid in neurogenesis in the hippocampus.

General physical activity and chronic antidepressant treatment have been shown to regulate levels of BDNF in the rat hippocampus. Studies from various laboratory experiments show that when mice and rats run freely on an exercise wheel, neurogenesis increases. This is measured by counting new cells, which are chemically marked in order to stand out. These findings in rat studies have been replicated in human research. A two-week study of the mice revealed changes in blood volume and blood vessel formation. Scientists were able to find a correlation between the growth of new neurons and the changes in blood volume. By applying a similar regime to a small group of middle-aged people, Columbia neuroscientist Scott Small found the same changes in blood volume, so were able to deduce that neurogenesis also occurs in humans, due to the similar hippocampal changes. Based on the findings, it is clear to see that some of the beneficial effects of exercise in aging individuals is mediated through dentate gyrus function, and in particular through neurogenesis.

However, it has been suggested (Gage, 2003) that there is a limit on BDNF production; mice which were bred to exercise showed higher levels of BDNF release, but it appeared that the levels reached a plateau by which further exercise had no change on BDNF production. It was
also found that the majority of the mice which were bred to over exercise showed an inability to learn, which is thought to be a result of a disruption of cognitive function, due to a fixation on physical activity.

A similar experiment was used to support the idea that exercise aids in the release of the neurotrophin BDNF. Griffin (2008) allocated sedentary 22 year old males into two exercise groups and a control group. Before undergoing training, the students watched a quick video of an array of stranger’s faces and names, to acts as a baseline for the later facial recognition memory task. When no students participated in exercise, there was no difference between the groups when the memory test was used. The two groups were asked to use stationary exercise bikes, one group taking part in moderate exercise for three weeks and five weeks, and another group undergoing intense, acute exercise for the same periods, and asked to pedal slowly and constantly until voluntary exhaustion. Blood samples were taken after exercise, and it was found that the control group (who remained rested throughout the study) showed neither a change in BDNF concentrations, nor memory after the face recognition task, whereas both exercise groups showed an increase in BDNF blood concentrations and in cognitive function.

The results showed that intense voluntary exercise enhances face and name matching skills, and these showed a positive correlation with the increase of BDNF. The experimenter also found that after three weeks training, no difference was found with exercise, although five weeks of aerobic exercise showed to increase fitness, cognitive function and serum BDNF response. This case study supported the hypothesis that BDNF increases levels of concentration, and hence the ability to learn new skills.

In order for exercise to be used as a way of promoting brain health with BDNF response, the type and duration of exercise would need to be determined and individualized to each patient. While some research (McGee, 2006) has illustrated that only intense exercise, such as treadmill running, where the heart rate is increased by at least 80 times the resting heart rate stimulates BDNF expression, other research suggests that light exercise routines may be sufficient to have similar beneficial effects. One argument puts forward the idea that intense exercise is likely to be more stressful, thereby cancelling the beneficial BDNF effects.

Recent studies (Rogas-Vargas, 2011) show that BDNF may play a part in energy metabolism and body weight regulation. This significant research documented that the higher the level of BDNF, the poorer the appetite, leading to greater weight loss.

Scientists (Unger and colleagues) recently explored the role of BDNF in energy regulation and eating habits by giving mice injections of glucose and measuring the volume of BDNF produced. They discovered that glucose leads to an increase in BDNF, indicating that the body signals to the brain to make BDNF when the body has taken in enough sugar. Researchers were interested in whether the cessation of the production of BDNF in an adult animal’s brain would reflect in the eating behaviours and voluntary exercise completed. By removing BDNF from the brain, they discovered that the removal of the protein resulted in the mice eating more and engaging in less voluntary exercise, so hence, become obese.

This study supported the conclusion that BDNF is important for energy balance and regulation, and the loss of production of this factor may lead to overeating and obesity, while
rodent studies are also supported by clinical evidence that polymorphisms in the BDNF gene are closely linked with eating disorders in humans. (Ribasés, 2003).

**Can exercise help reduce the risk of depression?**

A strong correlation has been found between exercise and good mental health. BDNF has been implicated in the pathophysiology of depression, in addition to both neuropsychiatric and neurodegenerative disorders (Greenberg, 2009). Decreases in BDNF have been reported in animal cases of depression and BDNF administration has proven to reduce depressive effects. Studies (McKimmie, 2005) show that physically active people are less likely to suffer from depression and are also more likely to recover from mild depression more rapidly. Individuals with depression have been found to have decreased levels of neurotransmitters serotonin and norepinephrine, while they have increased concentrations of cortisol in the hippocampus. Exercise is thought to increase levels of serotonin and norepinephrine by simulating the sympathetic nervous system. BDNF and serotonin have been found to be linked directly; BDNF creates an increase in serotonin production, whilst an increase in serotonin signalling enhances BDNF expression, known as the BDNF-serotonin loop. So, considering that BDNF and serotonin are reciprocal, it is likely that exercise will trigger the BDNF-serotonin loop, leading to potential mood improvement.

After multiple studies on rats showing depressive behaviours, it was discovered that a combination of both exercise and antidepressants could be used as treatment for depression, with the ability to reduce depressive symptoms faster than antidepressants alone. Antidepressants work by entering the bloodstream in order to reach the brain, where they affect the transmission of neurotransmitters, by increasing the availability of serotonin in the hippocampus. BDNF decreases depressive effects for a short period of time, whereas antidepressant drugs, such as fluoxetine decrease the effects of depression in the long-term. Researchers found that by combining exercise and antidepressants, they were able to increase BDNF production much faster than either treatment working individually; rats showed a decrease in depressive behaviours after just two days using both therapies, compared to two weeks when using antidepressants alone. This could be due to the fact that BDNF allows for more plasticity in neuron growth when patients are treated with antidepressants. Modern research is currently searching for successful alternatives to antidepressants, as studies show that only 1 in 3 patients respond to the first antidepressant treatment, while 2 in 3 patients respond to secondary treatment, which has resulted in BDNF being a highly active area of research, as it holds the possibility of becoming an alternative treatment for clinical depression.

In studies of depressed women (Sanders), it was found that their level of neurogenesis was up to 15% less than normal. This was also correlative research which found a link between the decrease in neurogenesis and the length of the period of depression, and found that induced neurogenesis may reverse the effects of depression. The time taken for antidepressants to take effect was almost equal to the time needed to induce neurogenesis, suggesting that BDNF is a key neurotransmitter in the brain and exercise acts as a trigger to stimulate BDNF production.

However, all research into how BDNF affects depression in both rats and humans has been correlation-based, thus we cannot obtain from data whether a disruption of BDNF signalling and related genes causes depressive behaviour, or whether it is a mere correlate. It would also
have been helpful to determine and regulate cortisol levels in plasma samples, as cortisol
dysregulation has been implicated in depression, in order to evaluate the possible role of
cortisol in the regulation of BDNF. There has also been questioning as regards the placebo
effect; whether the effects of depression are relieved due to knowing that exercise is likely to
improve mood.

**How BDNF increase affect the likelihood of developing Alzheimer’s disease**

It has been known for a long time that the hippocampus is sensitive to ageing. In humans,
serum and plasma BDNF levels decrease with advancing age, thus, the hippocampus decreases
in volume in older age, which further impacts on hippocampus-learning and memory tasks. It
is not a loss of hippocampal neurons which causes a reduction in the hippocampus, but instead
it is associated with reductions in: the branching of dendrites, spine densities, fibre density and
neurogenesis. Studies suggest that disturbances in the BDNF system also impact on
dysfunctions in the hippocampus, as proved with studies of depression and Alzheimer’s
disease. In humans, post-mortem examinations revealed lower levels of BDNF in the
hippocampus of older adults compared with younger adults (Brown). Furthermore, mediation
results of the hippocampus on aging memory decline were much more specific to the left
hippocampus compared to the right, suggesting that the different hemispheres play different,
yet complimentary roles in cognitive function. Experiments found that plasma BDNF levels
were negatively correlated with increasing age, which may be why the acquisition of new skills,
such as languages, dance and learning appear to be easier in younger people. It is likely that it
is the BDNF chemical which makes learning easier in younger people, which decreases with
increasing age.

The brain starts to lose nervous tissue at age 30. Studies show that aerobic exercise reinforces
neural connections by increasing the ability of dendrite connections between neurons, resulting
in an enhanced ability to process and store information.

Animals injected with a gene that produces BDNF showed improvements in thinking, memory
and learning. Brain cells that were expected to die, did not and brain cells that were
degenerated were revived when the animals were treated with the gene. The findings of this
research suggest that BDNF treatment could potentially slow or stop the progression of
Alzheimer’s disease.

Diseased neurons contain plaques containing aggregates of a protein called amyloid which
derives from an amyloid precursor protein (APP) found in neurons and other cells. Abnormal
catabolism of APP results in the formation of insoluble plaques outside the neurons. Mutations
of the APP gene are thought to be associated with the early onset of Alzheimer’s.

Mice which were genetically altered to produce amyloid plaque, and hence develop Alzheimer’s
disease were put on an exercise treadmill for 16 weeks (Um H. S, 2008). The results from this
experiment showed that factors relating to the formation of amyloid plaque were significantly
reduced and the exercise proved to stop multiple brain signals that induce brain death. The
BDNF protein was also elevated, suggesting that exercise helped to protect brain cell damage
and restore antioxidant function in brain cells. In the brain cells, the stress defence system was enhanced, showing they had a better average ability to tolerate stress. Other studies show that the mutation of the BDNF gene results in an increased vulnerability to stress.

BDNF is produced in the entorhinal cortex, an area of the brain that supports memory throughout life, and people with Alzheimer’s disease produce less of this substance. Reduced BDNF results in the shortening of axons and their branches that neurons use to connect to each other, and when this connection is lost between neurons, the neurons die. Alzheimer’s disease primarily affects the hippocampus, by damaging the brain cells connected with memory. BDNF acts directly on damaged cells in specific memory circuits in the brain. A series of studies showed that BDNF targets cortical cells, by preventing their death, stimulating their function, and improving acquisition of knowledge and cognizance. Therefore, BDNF treatment may be used to prevent disease progression in certain areas of the cortical region.

Animals treated with BDNF performed better on a variety of tasks involving the hippocampus, including memory and learning tasks. In the animals treated with BDNF, the brain cells in the hippocampus were notably enlarged and showed stronger connections with neurotransmitters, a sign that brain cells, and hence memory was being preserved. Once long-term trials show no decline in the health of the animals under treatment, researchers predict trials may then take place in humans, especially in cases where the risk of developing Alzheimer's is high, for example in hereditary cases.

Current experimental treatment for Alzheimer’s disease targets beta-amyloid production. In mice, the beneficial effects of BDNF treatment relied on the build up of this protein, which unfortunately, is thought to be toxic to the brain and form the foundation of Alzheimer’s disease. However, research into increasing BDNF is of great interest, as the protein is suggested as potential treatment, as the protective and restorative effects of BDNF on damaged neurons and neuron signalling may offer new approaches in treating Alzheimer’s disease. In addition, BDNF targets different mechanisms other than amyloid modulation, meaning that there is potential to combine both BDNF and amyloid-based treatments to create prolonged protection against the disease.

Evidence from patients with Alzheimer’s show significantly diminished acetylcholine transferase activity in brains. Acetylcholine transferase is an enzyme which synthesises acetylcholine by transferring the acetyl group from acetyl CoA to choline. Analysis of brains with Alzheimer’s show abnormalities in the neuronal parts of the brain, such as the cerebral cortex, which holds a vital role in memory and processing complex memory material. Synapses using acetylcholine are known as cholinergic synapses, which occur in many parts of the nervous system, including the brain. In certain people, the cluster of cells in the brain which produce acetylcholine degenerate as they become older, resulting in a shortage of acetylcholine in brain cells. It is this which causes the progressive deterioration of memory, as seen in Alzheimer’s disease. Current research focusing on treating Alzheimer’s disease has investigated inhibiting acetylcholinesterase in an attempt to retain normal levels of acetylcholine for as long as possible.

Loss of BDNF has also been suggested as a risk factor in the development of chronic diseases such as Parkinson’s and Huntington’s diseases. Research suggests that exercise represents a
practical and beneficial strategy for people suffering from Alzheimer’s disease. Moreover, the research suggests that exercise has the potential for use in strategies of treating other chronic diseases including diabetes, cardiovascular and Parkinson’s disease.

Some particular types of antidepressant, for example citalopram, uses selective serotonin reuptake inhibitor (SSRI) to raise BDNF levels, by causing an increase in serotonin levels, which cause nerve cells to release more BDNF. Therefore, SSRIs are under investigation for the potential to slow the progression of Alzheimer’s disease.

CONCLUSION
BDNF is currently a very active area of research in science. The unique ability the BDNF hormone has to aid in neurogenesis, neuronal growth and electrocognitive activity increases the likelihood of a treatment for Alzheimer’s disease, as research is advancing rapidly, which could lead to many improved lives in the future, once experimental research has been tried, tested and approved for multiple uses. Another possibility is the treatment of depression, by using the BDNF-serotonin loop to regain regular levels of serotonin in the nervous system and hippocampus. The results of studies showing the increased BDNF levels using antidepressant drugs and the antidepressive effects of BDNF in mouse models of depression suggest a vital role for this protein, its transmissions and receptors in the molecular mechanisms of depression therapy. The effects of BDNF are beneficial in terms of development and synaptic neuroplasticity by encouraging neurogenesis, suppressing apoptosis and modulating synaptic activity via a variety of signals.

Dendritic BDNF release is dependent on physical activity and the release causes an increase in presynaptic vesicle cycling, which stimulates synaptic activity further. Considering that BDNF stimulates neurogenesis and neuron growth, the effects of this research is studied further with the establishment of additional excitatory synapses.

In addition, a critical association regarding age-related hippocampal volume loss, cognitive performance and reduced levels of circulating BDNF in the brain has been established. The findings determining hippocampal volume loss in late adulthood is a critical area of research, as it suggests that increased concentrations of BDNF may help prevent volume loss. Further research is required to convincingly establish a causal relationship between declining levels of BDNF and hippocampal decay in late adulthood. It is also critical for future research to outline the potential for healthy lifestyles, including exercise to regulate BDNF levels in order to maintain healthy, hippocampal cognitive function.
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