Using BDNF to Treat Alzheimer’s Disease.

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DISTINCTION

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ABSTRACT
My paper focuses on the link between exercise and levels of brain-derived neurotropic factor (BDNF) in the brain. I will look at research showing the effects of BDNF in the brain, how it can improve cognition and memory through stimulating dendrite growth and neurogenesis, and will link this to its potential as a treatment for Alzheimer’s disease. Through the use of current research and my knowledge of Alzheimer's and the brain, I have formed theoretical ideas for the uses of BDNF and future developments of this exciting and relatively newly discovered protein. I shall explore the benefits and risks associated with such a treatment, as well as describing the ethical issues surrounding its use. Exercise, its role in producing BDNF, and how this may be pushed in the future, will also feature in my paper.

INTRODUCTION

The brain is the control centre of the human body, consisting of approximately 100 billion neurons that link together to form neuron networks. Neurons are composed of a cell body, or soma, from which protrudes the axon, a long projection that transmits electrochemical impulses away from the cell body. Dendrites are the branchlike extensions found at either end of the cell and they allow the cells to communicate with each other via synapses[1]. Here, the electrochemical impulse travels down the axon of the presynaptic cell, stimulating the release of the chemical neurotransmitter across the synaptic cleft, shown clearly in figure 1. The neurotransmitter binds to receptor sites on the surface of dendrites on the postsynaptic cell, where ion channels are opened and the chemical message is transformed back into an electrochemical impulse to be transmitted to the soma. Each time we learn something different we make new connections between neurons. These connections grow stronger every time we revisit that information, making it easier to recall. Eighty per cent of the signals in our brain are controlled by two neurotransmitters; glutamate, which stimulates the flow of impulses, and gamma-aminobutyric acid which inhibits impulse activity[3]. Brain-derived neurotropic factor (BDNF) is a chemical produced in the brain that has been found, not only to increase the number of receptor sites on neurons and cause dendrite growth, but also to stimulate a process called neurogenesis, the production of new neurons. BDNF can, consequently, improve our memory and make us more intelligent.

Owing to the affect that BDNF has on the brain, there are many studies in progress and hypotheses being investigated as to the possible uses of this chemical, especially of its potential medical roles. Scientists are looking into producing BDNF artificially, which will be necessary in the focus of my study, the use of BDNF as a treatment for Alzheimer’s disease. However, there is a way that our bodies can produce BDNF naturally, as first shown in the study by Cotman (1998)[4]. He divided mice into 4 groups, according to the number of nights they would run for, zero, two, four and seven. The mice were injected with a chemical that binds to
BDNF and their brains scanned. It became apparent that the mice that ran more had significantly higher levels of BDNF. The increased levels occurred in the hippocampus, the area of the brain that is largely responsible for much of our long-term memory. Cotman’s experiment proved the link between exercise and BDNF production. The relationship between the degeneration of the hippocampus and many age-related mental illnesses, such as Alzheimer’s disease, has given rise to the question of whether brain-derived neurotropic factor could be used to treat such conditions.

Alzheimer’s disease (AD) is the main cause of dementia and, according to Bupa’s health information team (2011)\(^5\), there are around 460,000 sufferers of AD living in the UK. It is a progressive disease, generally affecting older people, and it currently has no cure. The number of Alzheimer’s patients is rising due to our aging population. AD commonly causes memory loss, a shift in behaviour and emotions and an inability to perform simple daily activities. These symptoms are all as a result of brain deterioration, caused by the build-up of amyloid plaques and tau-containing tangles\(^6\). Plaques are deposits that surround the neurons, while tangles accumulate within nerve cells, leading to the shrinkage and death of neurons, as shown in figure 2. Mark Tuszynski and his research team (2009)\(^8\) investigated the effects of administering BDNF into amyloid-transgenic animals. They observed that many of the symptoms that they had induced in the animal due to the amyloid gene, such as the synapse loss and abnormal gene expression, were reversed when treated with BDNF. The researchers said, “In each case, when compared with control groups not treated with BDNF, the treated animals demonstrated significant improvement in the performance of a variety of learning and memory tests”. BDNF could be a breakthrough treatment for Alzheimer’s disease and dementia.
DISCUSSION

Age-related conditions that result in cognitive decline are becoming highly prominent in today’s society. According to the 2011 census, 1 in 6 people in England and Wales are over the age of 65, and therefore classed as elderly\(^9\). People who have already had a diagnosis of AD are likely to deteriorate rapidly with age, and for those who have not, the probability of developing AD increases dramatically as they get older. My proposal, owing to its positive effects on the brain and the encouraging results from Mark Tuszyński’s investigation (2009), is for brain-derived neurotropic factor to be produced artificially, exogenously, and then be administered to sufferers of Alzheimer’s disease and dementia.

It has already been shown that BDNF can be artificially synthesized outside the body. Several of the more recent research projects have focused on the possibility of injecting BDNF into the brains of rodents, observing the effects and how they could link to a treatment for Alzheimer’s disease. Arancibia’s investigation, “Protective effect of BDNF against beta-amyloid induced neurotoxicity” (2008)\(^{10}\) showed that BDNF completely reverses the toxic effects of some amyloid beta proteins, the main component of the plaques formed in AD, and partially reverses the toxic effect of other amyloid beta proteins. Figure 3, a graph from this investigation, shows that by increasing BDNF levels in the brain the toxic effects of certain forms of beta amyloid can be reversed, as the cells become more viable with increased BDNF concentrations.

![Figure 3: Graph showing BDNF’s reversal of the toxic effects of some forms of beta amyloid.\(^{10}\)](image)

This study supports the “neuroprotective properties” of BDNF and is a promising step towards its use as an AD treatment. The investigation by Dishman et al, “Neurobiology of Exercise” (2005)\(^{11}\), even found that “chronic activity wheel running has also been accompanied by decreases in extracellular amyloid plaques (in rats)”\(^\). Dishman’s team found that BDNF actually started to cure, not just the symptoms, but the disease itself.

Currently research seems to be focused on injecting brain-derived neurotropic factor into the brain itself. Clearly, if BDNF is going to be a viable form of medication, this is not a practical way to be introducing it to the body. One of the problems involved with delivering drugs designed to work in the brain, from outside the central nervous system, is the blood-brain barrier (BBB). BDNF would be too large to pass through the BBB and therefore would be ineffective, as it would not reach the brain. Techniques that have been used in the past include
making the drugs more lipid soluble, to allow them to pass through the endothelial cells in the brain. There have, however, been more successful methods of penetrating the BBB. A research team in Taiwan, led by Kuo-Chen Wei, who published an article in Chemistry World (2010)\textsuperscript{[12]}, found that they could inject magnetic nanoparticles, coated with a drug, then use ultrasound to open the BBB and guide the particles to a specific region, represented by figure 4. The experiment was carried out as a way of breaking through the BBB to treat brain tumours, but Kullervo Hynynen from the University of Toronto Medical School reported, “Ultrasound could also help in conditions such as Alzheimer's and Parkinson's”\textsuperscript{[12]}. Another possible way of getting BDNF into the brain, from outside the BBB, could be to inject it along with a hyperosmotic solution. This would draw water out of the endothelial cells, causing them to shrink, and allowing the BDNF to pass into the brain\textsuperscript{[13]}. These techniques, along with others, could be investigated further to allow the potential of administering BDNF either orally, or via self-injection in a more practical region.

As with many processes in the body, the way in which BDNF works is complex and has many factors influencing it. For learning and memory to be most effective it requires other hormones to work with BDNF to promote stem cell division. These hormones include IGF-1 (insulin-like growth factor), VEGF (vascular endothelial growth factor) and FGF-2 (fibroblast growth factor). As Ratey describes in his book, “Spark!” (2009)\textsuperscript{[3]}, “FGF-2 helps tissue grow, and in the brain it’s important to the process of LTP” (long-term potentiation) so these hormones obviously play an important role in memory and cognition. This leads me to believe that there may be a case for giving these hormones, along with BDNF, to sufferers of AD. A combination treatment may provide the prospect of more effective, and longer term, improvement in symptoms, especially in patients who are largely immobile, as these hormones are produced during exercise. Very frail or disabled people suffering from AD, who physically cannot exercise, may find treatment with these hormones gives them a better response than simply treating with BDNF. Again, further testing and studies could confirm, or rule out, any benefits of combined medication.

One future development I have looked into, is the possibility of reducing the chance, or at least the severity, of cognitive decline after surgery, in patients with, or at risk of, Alzheimer’s disease. It is well recognised that patients, especially the elderly, can suffer from a lasting cognitive decline after they have an operation and the likelihood is dramatically increased for Alzheimer’s patients. Tang et al (2013) performed a study entitled “Modulation of Murine Alzheimer Pathogenesis Behaviour by Surgery”\textsuperscript{[13]}. They put Alzheimer transgenic mice under anaesthesia and performed surgery on a proportion of these mice. They did the same to a control group of wild-type (WT) mice without AD. The results showed the influence of surgery in the transgenic mice caused cognitive impairment that persisted long after the operation, much more so than in the transgenic mice which only had anaesthetic. This is supported by the graphs in figure 5, which show a marked rise in the levels of beta amyloid and tau in the transgenic mice following surgery. There was no cognitive difference between
surgery and anaesthetic in the WT mice. Their conclusion was, “Surgery causes a durable increment in Alzheimer’s pathogenesis”.

It is not fully understood why surgery has this effect but it is thought that the stress and general inflammatory response of the body, which can worsen the effects of the protein plaques and tangles, are partially responsible. A decline in BDNF is seen in Alzheimer’s patients, but can also be produced by stress. Lower BDNF levels are linked to cognitive decline and so, from the research I have seen, I believe it may be possible to reduce the severity of cognitive dysfunction following surgery, if the patients with Alzheimer’s, or who are at risk, could be treated with BDNF before their operation, and possibly post-operatively as well.

The potential for problems to occur, due to artificially increasing BDNF levels, is yet to be evaluated. As with any drug, there are likely to be side effects to this treatment that would have to be investigated further. Should, however, future developments lead to a successful treatment for Alzheimer’s disease, the benefits to society and individuals could be huge. In the early stages of AD simple forgetfulness can be irritating and hinder everyday life, but later on the sufferer may well lose the ability to be independent, forget those closest to them and need full time care. A treatment such as BDNF, that could reverse damage in the brain, would massively improve the quality of life for Alzheimer’s sufferers and limit the pressure on family members and carers. It could dramatically reduce the helplessness and isolation that many people feel with this condition, enabling far more elderly people to be active members of society once more.

Treatment, that can alter the way we think and remember, could have an immense impact on the medical world, but it comes with its own ethical issues. Some may argue that having such a drug widely available could lead to its abuse. Those without mental deterioration may take it as an ‘intelligence drug’. In the wrong hands increased memory and improved intellect could be dangerous and, at best, just unfair that someone may gain academic advantages by ‘cheating’, much like a sportsperson using performance enhancing drugs in competitions. Furthermore, the funding for synthesizing BDNF and finding the mechanism to safely administer it, then producing the trials and studies to show its efficacy will be huge. For example in Carl Cotman’s first study on exercise and its link to BDNF, the simple running wheels for the mice cost $1,000 each [3b]. Many people would say that these funds should be directed to finding cures and treatments for diseases affecting younger people, as a large proportion of those with AD will have already lived long and full lives.
There is also an ethical issue concerned with testing on animals as producing a drug of this calibre involves significant animal testing (figure 6). Numerous people feel very strongly that it is wrong to make animals suffer to benefit humans. Having so many people suffering from Alzheimer’s disease in the UK means that, if BDNF was found to be an effective treatment, demand would huge. We would need to ensure that we have the supply to be able to treat everyone and the economic impact of this could be very large. It may put strain on the NHS and it is quite possible that cuts would have to be made elsewhere. This forces the ethical issue of who is more worthy of treatment, or whether other areas, such as salaries, should suffer because of this new medication.

There are, of course, many ethical arguments for the use of BDNF as a treatment for Alzheimer’s disease. The economic cost of testing and trials to produce the drug, as well as the cost of dispensing it, may be balanced out by the money saved on carers, reduction in care homes and increased numbers of people working longer, as they can continue to work with the condition, or staying in work because their relatives can cope on their own. It may even turn out to be a cost effective arrangement. Other ethical arguments are heavily based on the quality of life of people with Alzheimer’s. Just because it is generally a condition affecting older people does not mean that we should not try and treat it. Many believe elderly people have just as many rights as anybody else, and this includes their right to be treated. Not only this, but AD is actually becoming more common in younger people too. Some as young as 40 years old are being diagnosed with the condition, which makes it more crucial than ever to have an effective treatment that can slow down the disease progression.

The UK has an aging population so there will be a big rise in AD cases. Many working family members will come out of their jobs to care full time for elderly relatives with AD, which is not only stressful for themselves, but it reduces the numbers of people contributing to the economy and depletes the budget available for pensions and other important government funds. A drug such a BDNF could improve the cognitive health of a huge proportion of elderly people with Alzheimer’s. Research by Ehlers A. (2011) into elderly volunteers shows that in the UK 30% of 65-74 years olds volunteer on a regular basis and 20% of people over 74 years of age[15]. Their volunteering is hugely important economically and socially, the figures suggest that elderly people want to be involved in society and contributing. If we could eliminate those restricted by AD and dementia I believe these figures would rise substantially, which is a significant ethical argument for the use of BDNF.

Although there is much research currently studying artificially producing BDNF as a treatment, there is no escaping from the fact that brain-derived neurotropic factor can be produced naturally. I think that future advances surrounding BDNF may focus around using exercise to naturally increase levels in the brain. Developments may include GP recommendations, exercise classes targeted specifically at Alzheimer’s sufferers and even new forms of training machines to target the precise forms of exercise that will best improve cognitive health. I think the research into exercise and the brain will have an impact on the medical world as patients...
visiting the GP for conditions such as depression, stress, ADHD, even AD and dementia, could be sent away with a ‘prescription’ for exercise. In a study by Zheng et al, “Beneficial effects of exercise and its molecular mechanisms on depression in rats” (2006)[16] the team exposed rats to chronic unpredictable stress (CNS) for 4 weeks, one group had access to voluntary wheel running, while the other did not. The study stated, “CNS significantly decreased hippocampal BDNF mRNA levels. However, voluntary exercise improved or even reversed these harmful behavioural effects in stressed rats.” This shows the positive effects of exercise and BDNF production in improving conditions such as stress and depression.

The type of exercise undertaken can also have an effect on the levels of BDNF in the brain. A study undertaken by Greenough et al (2004)[17] measured the BDNF levels in two groups of rats. One of these had been taught complex motor skills, such as walking across unstable objects, and the other simply ran on a running wheel. After two weeks of exercising it was found that the rats who had learnt complex motor skills had a 35% increase in BDNF levels over the other rats. This supports the conclusion that sports that are skills-based will cause higher levels of BDNF in the brain. However other evidence such as the 2007 study by Winter and his research team showed that short bursts of intense cardiovascular exercise (figure 7) led to spikes in BDNF levels and the participants who exercised could learn a list of vocabulary words 20% faster than the control group[18]. The results of the two studies suggest that the best type of exercise for a person to do, in order to improve their condition, may not be straightforward. This complexity could lead to all sorts of developments, for example a new field of sports science, specific exercise groups for people with mental conditions to deliver a particular exercise plan that would give the best results for their brain. Along with this, new exercise machinery may become available that would combine the most effective forms of exercise, in order to target the body’s BDNF response mechanisms.
CONCLUSION

Alzheimer’s disease is a common and progressive, age-related disease that currently has no cure. My paper highlights the possibility of artificially synthesizing brain-derived neurotropic factor, produced in the brain during exercise, as a treatment, or even a possible cure, for AD. BDNF has been shown to have several positive effects on the hippocampus in the brain, including increasing the number of receptors, causing dendrite growth (figure 8) and stimulating neurogenesis. Alzheimer’s causes a spiral of negative effects in the brain, that lead to problems such as memory loss, reduced cognition and mood swings. The overriding cause of these symptoms is neuron death, which is what makes BDNF such a suitable candidate for research as an AD drug. In my paper I also explained the potential future development of BDNF for reducing cognitive decline in Alzheimer’s patients following surgery. If this process were to be viable then it may open up many other possible uses for BDNF in medicine.

There are problems with my idea to use BDNF as a treatment for Alzheimer’s. One of these is that avoiding injecting BDNF into the brain means that it will have to pass across the blood-brain barrier to reach the regions where it can be effective. There is new research into ways of penetrating this barrier and in the future, ultrasound or hyperosmotic solutions to produce temporary holes in the blood-brain barrier maybe very real solutions. Another potential problem is that it is unclear how long the effects of BDNF will last. Alzheimer’s is a progressive disease so, from the point someone starts treatment, they are likely to need it lifelong. Also, if the effect of BDNF medication is very short-lived then a person may have to take several doses a day. BDNF is produced by the BDNF gene, and therefore, a very theoretical solution to this problem, that may be explored in the future, is the possibility of BDNF gene therapy; either introducing or attempting to change the existing genes, that have diminished function in Alzheimer’s patient’s brains, with genes that can once again stimulate the process of BDNF production. This may be a more permanent solution.

Although artificially producing BDNF may ultimately be a suitable solution for Alzheimer’s disease, I also recognise that there are other, natural ways, of delaying the onset of this condition. Exercise causes BDNF to be produced in the brain, leading to better cognition and memory. One of the problems, at present, is that there has not been adequate research into the type of exercise that best improves BDNF levels. I believe this will be a popular topic of research in the future and developments of exercise plans, GPs recommending exercise and other new fields of study are all likely to be seen.
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