Exploring the Possible Role of BDNF in the Prevention and Treatment of Alzheimer’s Disease

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ABSTRACT

We have noted that brain-derived neurotrophic factor (BDNF) aids the formation of receptor sites for synapses on neurons in the brain, and more receptor sites can improve memory and learning ability. Studies have shown that BDNF production is increased by exercise; however, due to the poor mobility of many sufferers of Alzheimer’s Disease, we have investigated other possible methods of increasing the amount of BDNF which circulates in the body. These include stimulating the production of BDNF in the body using methods other than exercise, such as by the introduction of curcumin into the body, or the use of anti-depressant drugs. We have concluded that these two methods could potentially increase BDNF levels in the brains of people with Alzheimer's Disease, and that these methods could become part of a national treatment programme to alleviate some of the symptoms of the chronic illness for thousands of people across the UK.

INTRODUCTION

Brain-derived neurotrophic factor (BDNF) is a protein and a neurotrophic growth factor. It is a protein found in the brain and peripheral nervous system that encourages synaptic growth and the development of new neurons. Although its exact mechanism of action is unclear, it is thought to have an effect on neurotransmitters. It binds to neurotrophic receptors including TrkB and LNGFR; these affect nerve growth. (Meek, Patrick D. et al., 1998)

Altered levels of BDNF have been associated with a number of neurological conditions including Alzheimer Disease, depression, schizophrenia, dementia and anorexia nervosa. BDNF is normally produced throughout life in an area of the brain known as the entorhinal cortex that is important for memory. People with Alzheimer's make less of the substance. Animals treated with BDNF performed better on a variety of learning and memory tasks. Notably, brain cells in the hippocampus, a portion of the brain critical for memory, were larger and showed stronger connections; these are signs that memory and other thought processes were being preserved. The hippocampus is one of the first areas of the brain damaged by Alzheimer's disease.

In Alzheimer’s disease, lower levels of BDNF have been reported. There are approximately 30 million sufferers of Alzheimer's worldwide and it is predicted that by 2050 it will affect 1 in 85 people globally; therefore the disease is of massive public health concern. Furthermore Alzheimer’s in the United States costs around $100 billion per annum (Meek, Patrick D. et al., 1998). With the massive impact of the disease on individuals as well as economies across the world in terms of public health, there is sizable pressure on the research community and the pharmaceutical industry to investigate any lead which may come up with a plausible treatment to this debilitating disease.

As BDNF appears to be modified in Alzheimer’s, it creates a tangible opportunity for the research community to impact detection, treatment and eventually potentially prevention of this disease. Many current experimental treatments for Alzheimer’s disease target beta-amyloid production, so the potential role of BDNF as an alternative protective intervention is of great potential interest. Because BDNF targets a different set of disease mechanisms than amyloid modulation, there is also potential to combine BDNF and amyloid-based treatments, theoretically providing a two-pronged attack on the disease.
Research suggests that BDNF stimulates neurogenesis in the adult brain (Scharfman H., et al., 2005). There is evidence linking BDNF production with exercise (Oliff H. et al., 1998) and once produced BDNF can remain in the brain for up to two months (Molteni R. et al, 2004).

DISCUSSION

As BDNF is altered in a number of disease states, it lends itself to the possibility of being a biomarker for the detection and particularly the progress of disease in any one individual. This could have immense impact in a disease population where late detection means that often the treatment is provided far too late to make a difference to an individual patient. Use of a biomarker in diagnostic tools is not a new phenomenon but has considerable interest these days, as the medical community is ever more interested in targeted therapies for individualising patient treatment.

The definition of a biomarker is “an indicator of a biological state. It is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”.


Diagnostic tests have been employed for many years to identify a relevant patient population, exclude them from a potential treatment or enhance the use of therapeutic products. Tests are also used during therapeutic drug development to obtain data used to assist in the decision making for Regulatory Authorities which approve drugs. After a therapeutic product is commercially available for use, health care professionals may use a relevant diagnostic test, for example, to select the appropriate patient for a particular therapy or to optimize a dosing regimen.

More recently, the development of therapeutic products that depend on the use of a diagnostic test to meet labelled safety and effectiveness claims has become more common. For example, such a test can identify appropriate subpopulations for treatment or identify populations who should not receive a particular treatment because of an increased risk of a serious side effect. One reason for increasing interest is the emergence of new technologies that can distinguish subsets of populations that respond differently to treatment, thereby identifying patients who are most likely to respond, or who are at lower or higher risk for a particular side effect.

The development of BDNF as a biomarker for use in a diagnostic test could be essential for the safe and effective use of a drug therapy in order to identify patients who are most likely to benefit from a particular therapeutic product; to identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product; to monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation), to achieve improved safety or effectiveness. Due to the high cost of BDNF treatment, it may only be possible to treat people who have Alzheimer’s disease which has developed to a certain severity. Diagnostic tests could be carried out involving using BDNF, to see at which point the treatment would be most effective and make the greatest difference to a person’s quality of life. The group to which treatment has the greatest positive effect would then indicate that people with that stage of Alzheimer’s Disease would benefit from the treatment the most, so should be offered the treatment first.
This poses the question as to whether or not the treatment would be offered by the NHS, or if people would have to pay for it privately. If many more studies are carried out to prove the effectiveness of BDNF in improving memory and learning in people with Alzheimer’s, this could provide the necessary evidence to propose that the treatment is offered by the NHS, due to the improvement it would make to the lives of the many people with Alzheimer’s in the UK.

The drug development process is extremely lengthy, costly and risky, with very high levels of failure. Early stage research is often undertaken in academic institutions where basic concepts of types of structures of biological or chemical compound which may have an effect on a biological target are worked out. In the case of BDNF the types of areas the researchers may look to explore include areas such as how BDNF is produced; how it is regulated ie. what impacts higher levels of production of BDNF; what inhibits BDNF; what interacts with this protein to impact its behaviour. For example it is reported that increased levels of physical exercise in humans increased blood levels of BDNF. Through exploring how exercise physiologically impacts the production or regulation of the BDNF protein, scientists may be able to see how pharmacologically such behaviour can be mimicked and use this as the basis of how to design new drugs which target BDNF upregulation, for example. Knowledge of such target features allows scientists also to undertake high throughput screening – where thousands of potential drug structures are tested against such targets and where positive results, known as “hits”, inform decisions about what chemical or biological structures may need to be intrinsically part of a potential drug candidate. Potential structures are taken through multiple tests to explore further how it might be improved to increase its ability to impact the physiological target, as well as tests to understand and characterise features of these “drug candidates”. Armed with knowledge of what features characterise a molecule in standardised tests, these are compared and the most promising taken forward into the lengthy drug development process. At this stage pharmaceutical companies are usually involved to fund the complex development studies initially in two species of animals and then in humans. Many potential treatments for Alzheimer’s disease disappointingly fail in the trials in humans as the complexity of the clinical presentation and manifestation of the disease is so interrelated, although one feature of the disease may be impacted, others may not and therefore Drug Regulators are reluctant to give approvals in such cases.

Given that the entire drug development process can take 15 years or longer there may be alternatives which allow for a faster route to approval – that is where drugs which are known to work in one disease are used in another disease. A relevant example here might be the use of certain antidepressants which have been shown to elevate BDNF levels. If these drugs are already approved by the Drug Regulators, then the majority of the costly and lengthy trials, particularly the animal and the safety studies, can support the development in Alzheimer’s patients. Speculatively this might reduce the work needed to get an approval down to two pivotal trials in the target population which may be conducted in around 3 years. This alternative approach gives an exciting opportunity for an early treatment to be found.

There is interest in the scientific drug development community in the possible therapeutic application of BDNF in modifying fundamental processes underlying neural disease, given the diverse presence and activity of BDNF which suggests a potential role for this molecule in the pathogenesis and treatment of both neurological, psychiatric and neurodegenerative disorders such as Alzheimer's disease.
So-called BDNF “Copy Cats” have been looked at to assess their clinical application in patients; however it has been seen that by using BDNF itself has many issues in including the fact that it has a short half-life and low rate of transport across the blood–brain barrier. Nonetheless data from University of California showed that in animal experiments on mice and monkeys, when BDNF was administered to memory circuits in the brain, their activity was directly stimulated and cell death from the underlying disease was prevented. The fact that BDNF does not work on amyloid protein but by alternative pathways gives the potential for multiple routes of attack when impacting neurodegenerative processes.

One possible method of increasing the amount of BDNF in the body is by natural methods which stimulate the body’s production of the chemical. Slight sleep deprivation in rats can increase the amount of BDNF in the body compared with a normal amount of sleep (Cirelli et al. 2006). Slight sleep deprivation could therefore potentially have the same effect on BDNF production in humans. However, sleep deprivation has many negative side effects, such as a weakened immune system, and slower reaction times. It would therefore not be wise to recommend sleep deprivation to increase BDNF levels in the hope of improving memory and learning. Another study has shown that curcumin, a curry spice which has anti-oxidising properties, can normalise BDNF levels when they have been reduced (Huang et al. 2001). Corticosterone (CORT) was used to create a state of depression in rats, with the side-effect of a decrease in the amount of BDNF in the hippocampus and frontal cortex regions of the brains of the rats. Curcumin was given to the rats, and this increased levels of BDNF in these areas of the brain greatly (see Fig. 1). The diagram shows that rats administered with curcumin had BDNF levels in the hippocampus and frontal cortex which returned almost to the normal level shown by the control group, which had not been given corticosterone. Studies could be done on the effect of curcumin in humans with Alzheimer’s Disease, to see if the same result of an increased level of BDNF in the brain can be obtained. A study involving administering curcumin orally in tablet form was done as a Phase II M D Anderson Study, when investigating the effects of curcumin on cancerous tumors. (Leon, 2008). This study claims that “curcumin normally is poorly absorbed” (Leon, 2008) in the digestive system. Therefore if a more effective method of curcumin administration could be used, the positive results of an increase in BDNF levels could be maximised. It has been suggested that a lipid capsule could be created to surround the curcumin, so that the
curcumin could enter the bloodstream (Leon, 2008). Alternatively, we suggest that an intravenous method of curcumin administration could be developed, to increase the amount of curcumin which successfully enters the bloodstream.

Treating disease versus preventing a disease requires a rather different approach when developing drugs; treatment focuses on detection and monitoring for improvement of certain symptoms or biomarkers, while prevention is much more like a vaccine, in that it focuses on giving a drug in the absence of symptoms and monitoring for emergence or lack of emergence of symptoms. It may be that the prevention route is tailored to look specifically at those people who are most at risk of developing Alzheimer’s, maybe because they possess either a strong family history of the disease, or have a certain gene as an indicator even in the absence of family history. The key feature of a preventative treatment is that it must be safe over the long term as these are essentially healthy people and the risk-benefit ratio is different than when a drug is given to a patient with a confirmed disease.

One factor which must be considered when contemplating giving BDNF treatment to a patient is the ethics of the treatment. People with Alzheimer’s Disease often do not have the mental capacity to use proper judgment when making choices regarding treatment for their disease, or are unable to communicate their desires for treatment; this leads to the question of whether BDNF treatment can be administered to these people without their direct consent, for the benefit of their health and therefore improved quality of life. A possible solution to this would be to have a standardised procedure of a patient being asked when they are first diagnosed with the disease if they would like to receive BDNF treatment when their disease progresses into later stages. This would allow many people to state their desire to receive or not receive the treatment well in advance of possibly having treatment, allowing them to make the decision themselves. However, if the patient has not specified whether they would like treatment or not, the family of the patient could be consulted about whether or not they would like the patient to receive treatment. If the patient has no remaining family, it may then be necessary for an independent group of medics to decide whether or not treatment should be given.

CONCLUSION

Many studies have shown that brain-derived neurotrophic factor can improve memory and learning, and can therefore reduce some symptoms of people with Alzheimer’s disease. We believe that the administration of BDNF to people with the disease could become a widely-used treatment for Alzheimer’s in the future, improving the lives of many of the 496,000 people with Alzheimer’s disease in the UK. BDNF production in the body is stimulated by exercise; however, since many people with Alzheimer’s disease are elderly, and no longer have full mobility, it will not always be possible for people with the disease to exercise to raise their BDNF levels. We therefore have suggested that other methods be used to increase the levels of the chemical. One proposal is to stimulate BDNF production in the body using ways other than exercise, such as by the introduction of the spice curcumin into the body. Another possible method is to increase BDNF levels by using a drug which has already been approved to treat another condition, such as depression; this could reduce the number of clinical trials required before the treatment can be used for people with Alzheimer’s Disease, as the drugs would already be known to be safe. Treatment would require a large amount of funding, however the potential benefits of the treatment are significant; therefore the treatment would need to be as cost-effective as possible. One way of achieving this is by only giving the
treatment to those individuals who previously expressed that they would like it, since we have proposed that people should be asked when they are first diagnosed if they want the treatment if it is offered to them at a later stage, but they are no longer able to communicate their desires successfully. Another way of reducing the financial impact of introducing the treatment to the NHS would be to only administer the treatment to people who would gain the most benefit from it; the group of people who would have the most positive effects could be discovered using diagnostic tests. Many more studies into the effects of curcumin and anti-depressant drugs in humans with Alzheimer’s Disease would need to be undertaken to provide more substantial proof of the benefits and safety of the treatments; following this, a national treatment programme involving either the use of curcumin, anti-depressants, or a combination of the two, could be proposed.
REFERENCES


