Brain-Derived Neurotrophic Factor and possible applications in clinical medicine.

By:
Benjamin Samra
Pass with Merit

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

17th March 2013
ABSTRACT
During recent years a great deal of research has been done into the chemical mechanisms of the brain. In this paper I will discuss the possible applications of this research to clinical medicine in the near future. The main areas that are focused on are BDNF and its effect on neuron growth and applications in traumatic brain and spinal injuries, BDNF and neuron survival, how exercise effects BDNF levels and the possibility of using these as a treatment for neurodegenerative diseases and also the possibility of creating drugs to imitate the function or stimulate the production of BDNF.

INTRODUCTION
When the structure of the brain was first described and detailed the belief was that the brain was a fixed size and shape that it could not adapt, this is demonstrated by Ramón y Cajal (one of the founding fathers of neuroscience) who stated in 1928 that “once development is complete, the sources of growth and regeneration of axons and dendrites are irretrievably lost. In the adult brain nerve paths are fixed and immutable: everything can die, nothing can be regenerated”. This view however has been completely overturned in recent years and we now understand that the brain is a continuously growing and changing part of the human anatomy and that it has the capacity to do things that seem impossible, such as reversing paralysis as was demonstrated in the case of Pedro Bach-y-Rita who after suffering a severe stroke in 1958 which caused paralysis in one side of his body. Mr Bach-y-Rita was treated by his son Paul Bach-y-Rita and was eventually able to lead a normal life again, this at the time was a dramatic result as it demonstrated that the brain could adapt even at later stages of life. This ability to adapt is referred to as neuroplasticity.

Neuroplasticity is the mechanism by which our brains are able to change and adapt so that we can learn. Neuroplasticity occurs at many levels in the brain, at the cellular level the way in which neuroplasticity occurs is down to the making and breaking of connections between two or more neuron. The way in which this works is that connections that are not being used frequently effectively wither and disconnect, where as frequently used connections strengthen their connection by increasing the number of synapses between the two neurons involved. At the synaptic level the ways in which neuroplasticity occur are even more complicated. The first way that neurons can change their function is by altering how much signal they send to each neighbouring neuron, this can be achieved by changing the number of neurotransmitter vesicles going to each synapse or by changing the number of neurotransmitter chemicals in each vesicle. Another method is to change the number of active sites (the area where the vesicles release their cargo of neurotransmitters into the synapse) on each synapse. Further still each neuron can control how many neurotransmitter reuptake receptors there are and therefore the likely hood that the neurotransmitters are to make it across the synapse. Finally the neurons can control the number of calcium channels they have. Calcium ions are what cause the vesicles to bond to the synaptic wall and hence release their neurotransmitters and so the more calcium channels the more calcium ions and therefore the more signal transmitted to the next neuron.

The chemical mechanisms by which these changes occur is an area that scientist are still coming to understand. As they discover more and more about neuroplasticity one chemical that keeps reappearing is BDNF or Brain-Derived Neurotrophic Factor. BDNF is a member of the neurotrophin family, a group of similar chemicals that are responsible for neurogenesis and dendrite reorganisation and also this family of chemicals play a vital role in the development of the central and peripheral nervous systems. The way in which BDNF works is shown in Figure 1.
it triggers a high-affinity tropomyosin-receptor kinase (Trk) this receptor the sets of a cascade of chemical signals (see figure.1 for more detail) which ultimately finishes with the production of Ca2+ ions and other chemicals that ensure the neurons survival and also promote neurogenesis and outgrowth. The Ca2+ ions play a vital role in a very interesting part of the BDNF cycle and that is they promote the release of more BDNF. This is not a perfect cycle however and so eventually BDNF production stops until another stimulus set of the process again.

BDNF then is a very interesting chemical and it has recently been shown that exercise can lead to a boost in levels of BDNF (Gómez-Pinilla (2002) Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity). This is of great significance because the growth of neurons, specifically the dendrites, generates an increased capacity of the subject to learn and this has been shown to be true in both rats (Cotman (1998) Exercise-induced regulation of brain-derived neurotrophic factor (BDNF) transcripts in the rat hippocampus) and much more recently in humans (Winter (2007) High impact running improves learning). Research has also shown that a lack of BDNF could be causally related to degenerative brain disorders such as Alzheimer’s(Phillips (1991) BDNF mRNA is decreased in the hippocampus of individuals with Alzheimer’s disease) this is interesting as if true it could lead to a cure or at least a method of preventing further deterioration in these patients. It is not however all good as high levels of BDNF have also been associated with hyperexcitability and there are concerns that very high levels of BDNF could lead to seizures as all of you neurons start to fire more and more easily, however more larger and long-term studies need to be done on this phenomenon.

DISCUSSION
The research into BDNF and neuroplasticity in general has many applications to medicine; however the main areas that I will be discussing are its uses in recovery after damage to the brain or nervous tissue and its possible use as a preventative measure against neurodegenerative diseases. However before any of this research into how we can use BDNF becomes practical application we have to know how it is made and how to make it ourselves. The best current known way to improve levels of BDNF naturally is through exercise (as mentioned above) it has been shown through rat models that even after just six hours of voluntary levels of BDNF are significantly increased. It has also been demonstrated that this is not just a short term effect. Cotman showed that two weeks after a three week period of access to a running wheel were still 133% up from normal. The use of exercise is possible the best way of producing BDNF as it is natural to the body and is ultimately an extra bonus on top of a healthy life style.

There will however be some patients that cannot perform the exercise required to boost their BDNF levels significantly (such as spinal injury patients or patients that have not regained consciousness). For these patients then it is vital that we start looking for artificial ways of either stimulating BDNF production in the body or producing it externally and then injecting it into the blood stream. The first of these two suggestions has already received a bit of attention as is shown in the work of Jana A (2013) in it is shown that cinnamon and its metabolite sodium benzoate (NaB) increased the levels of BDNF in the brain. This amazingly lucky as cinnamon and NaB are both already approved food stuff and drug already this means that they have both already been declared safe for human consumption. Another advantage is that it has already been shown that the cinnamon can be administered orally this will reduce
complications and is of particular use in patients with weakened immune systems as there is little, if any, chance that they are going to get an infection from taking the drug. There are however some problems, firstly taking this will only stimulate BDNF production and so there could be a delay in the rise in level, secondly for it to be effective the active ingredient will have to be found and although cinnamon is a spice already consumed by some people the dosage required is unknown and whether there are any dangerous side effects at this concentration.

The final possible way to boost BDNF levels is to produce BDNF externally and then inject it into the patient. The major problem with this suggestion is producing the BDNF in the first place. The method I propose is similar to that of how insulin is produced. The BDNF gene has already been identified and so this removes a lot of the effort required to make this suggestion work. I propose that, like insulin, the gene for BDNF is transplanted into a bacterium’s plasmid in a position where there is normally a gene for another product that the bacterium produces into the environment. The bacterium should then theoretically produce BDNF which can then be purified so that it can be used. There are some problems still with this suggestion and they are that you cannot control where in the body the BDNF will go this is of significance as BDNF has been shown to play a role in energy homeostasis around the body and so injecting it into the blood stream could have unknown consequences. Furthermore there is the problem of the blood brain barrier which restricts diffusion of large molecules into the brain. This could be a problem because if BDNF is blocked partly or, in the worst case, fully by the blood brain barrier then an injection into the brain itself would be required and this would be highly dangerous. Overall then exercise it would seem is the best way to improve levels of BDNF as it has the least number of possible complication.

The first way in which BDNF could be useful in a clinical setting, is in trying to restore function to damaged nervous tissue. One of the most extreme cases that doctors see of damage nervous tissue is in traumatic brain injuries (TBI). TBI occurs when a person is hits there head there are three main stages to the injury the first is the initial impact which shakes the skull and therefore the brain, in the worst cases the skull is actually penetrated and the brain tissue ripped apart, this causes neuron death. The second stage is a reduction or even loss of blood flow to some or maybe all of the brain, this starves the tissue of oxygen and other vital molecules it needs thus compounding the damage from the first stage. The third and final stage does not necessarily occur directly after stages one and two but could occur at any point after them and involves possible haemorrhaging and other complications. Due to the complicated way in which TBIs occur there are different categories from mild to severe, further still the complexity of these injuries means that patients require care from a multidisciplinary team.

The current method for treating traumatic brain injury is surgery, to stabilise the patient, followed by a long period of intensive rehabilitation. I believe that there are two ways in which the current research into BDNF could be applied to help TBI patients. Firstly studies have shown that having increased levels of BDNF before an injury speeds up recovery afterwards. It has been suggested that BDNF plays a vital role in preventing neuron death and hence reduce the overall damage and speed up recovery. It would therefore be advantageous if patients had raised levels of BDNF prior to their accident; however it is not possible for a person to know that they are going to have an accident, and so artificially raising their BDNF levels just before the incident is not feasible. This means that the only way to make sure that people have high levels of BDNF prior to their accidents is to use exercise, as it has been show to raise levels of
BDNF and therefore a healthy, active lifestyle would be a good preventative measure against TBI. I would therefore suggest that doctors should encourage people to exercise even if they are already fairly healthy.

The second way in which the current research could be applied is post injury. At this point the primary objective (after stabilising the patient) is to try and recover as much function as possible. In order for the brain to recover this function it has to either grow more neurons or reconnect and rearrange existing ones. As BDNF is a major stimulant of neuron growth boosting its level in the brain could seriously reduce the length of recovery needed. This logically leads one to conclude that we should try to boost levels of BDNF in the brains of TBI patients. There is however a problem with this as currently the best known way to improve BDNF levels (as I discussed earlier) is by exercise and most TBI patients are unable to do this. It is for these circumstances that I propose that doctors use drugs that either stimulates BDNF production or an actual injection of BDNF itself.

Spinal injuries are much like TBIs in how the occur and in how they are treated. The major, and somewhat obvious, difference is that they occur on the spine and not the brain. This means that they are far more accessible for treatment. Again, as with TBIs, in most cases it would not be possible for the patient to exercise. So I again propose that they should use an artificial BDNF raiser, however in order to deliver the drug effectively I suggest if the patient requires surgery on the area of the spine affected that after the operation is complete but before closing the wound up they inject the affected area with either BDNF or a BDNF production.

Another similar situation in which BDNF would be useful is during replantation surgery. This is surgery to reattach a lost limb or other body part. One of the key moments in this kind of surgery is the reconnecting of the nerves. As this is key to the person being able to regain function in their limb I would again suggest that before closing the wound the doctors should deliver a small amount of BDNF to the reconnected nerves. This should help them reconnect theoretically as BDNF increases dendrite growth and promotes neuroplasticity.

A completely different way in which the current research into BDNF can be applied to clinical medicine is that of preventing neurodegenerative diseases. The United Kingdom currently has an aging population with over 10 million over 65 and that number expected to double in the next 40 years. It is not surprising therefore that incidents of Alzheimer’s and Dementia and other neurodegenerative diseases are on the rise. It clear that the prevention and treatment of neurodegenerative diseases is and will continue to be a major part of clinical medicine. In this paper I will take Alzheimer’s as a representative for all neurodegenerative diseases as I do not have the space to consider the whole host of diseases that exist. I believe however that, with subtle changes, the proposal I am about to outline can be applied to most of this kind of neurological disease.

Alzheimer’s is a neurological disease that is exhibited almost exclusively in the older population. Symptoms include confusion, speech problems and loss of motor co-ordination. The causes of the disease are not well understood however the most current view is that it is caused by plaques and tangles in the brain. The main problem with the disease is that by the time the diagnosable symptoms appear the condition is already very advanced. This is where I propose that BDNF can help; it has been shown that people suffering with Alzheimer’s have lower levels of BDNF and I propose that this could possibly be used as an advance warning.
system. There are of course problems with this as many factors affect the levels of BDNF and so in order to use this as a standalone diagnostic tool would be ridiculous however if taken into consideration with other symptoms then it could be valuable in catching the disease early. There is of course the ethical problems that are associated with trying to catch a disease early as demonstrated by breast cancer where there can be a tenancy to over diagnose. However this should be less of a problem as the current treatment for Alzheimer’s is less severe than that for breast cancer.

The current treatment for Alzheimer’s is a mixture of cognitive and physical exercise and a controlled diet this is kind of treatment is backed up by many studies theoretically should work in reducing the rate of decline as we know that a mixture of mental and physical stimulation are good ways to raise BDNF levels and improve neuroplasticity, however although these help prevent the decline of the disease nothing has yet been discovered to halt or reverse the effects of the disease. In this aspect the application of the research into BDNF maybe no better but this is no reason to disregard it but more a reason to try and push our knowledge further so that we may one day be able to beat Alzheimer’s and other forms of dementia.

CONCLUSION
In this paper I have tried to outline some of the ways in which I believe that research into how BDNF and other neurotrophins may be able to improve clinical medicine. To summarise the ways in which it could be applied there are two main ways it can be applied; as a preventative measure against neurodegenerative diseases, and post injury to try and improve and speed up recovery.

There are a few ethical issues I left out of the main text as they are common features of medical trials and research and development of new treatments; however I do believe that they do deserve a mention. Firstly the use of genetic manipulation is always a hotly contested area and while it is an issue I do believe it to be quite a small one in the case of the genetic manipulation of bacterium in order to supply us with the drugs we need as we have been doing so with insulin for the three decades now. Secondly the use of animals in the testing of drugs will of course be necessary for the development of safe drugs, this issue is trickier as there is a very fine line between scientific tests and cruelty. This can be safely navigated I feel by ensuring that all test perform on animals are relevant and will have some impact on the world of medicine. Finally the possible application for BDNF and its associated chemicals is near limitless and I hope that we see some of the ideas put forward in this paper come to fruition and that one day we may be able to remove at least the suffering from neurological illnesses.

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IMAGES
Figure.1 BDNF and the following cascade of activity.
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