Coffee, Cannabis and Exercise: Ingredients to the future cure for Alzheimer’s

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DISTINCTION

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

Date here:
March 2013
ABSTRACT

Dementia is a serious loss of global cognitive ability in a previously unimpaired person, beyond what might be expected from normal ageing. The affected cognitive areas can be memory, attention, language and problem solving. Dementia and its most common form Alzheimer's cannot be cured and is degenerative. This means the sufferer relies on close relatives for assistance. This is one of the reasons why Alzheimer's is one of the most costly diseases to society.

I have developed, following current research, a theory on how Alzheimer's could be potentially cured in the future. The theory is the use of cocaine, coffee and exercise on warding off this disease in elderly. I carried out a Gedanken experiment however; the research and case studies show that this potential cure is highly feasible.

INTRODUCTION

To understand how the body can influence and improve the brain, it is essential to understand how the brain works. The brain is made up of millions of cells called neurons. Neurons do not touch but interface at a junction called the synapse. Inputs enter a neuron via a number of dendrites. The inputs are converted to a single electric output which then travels along the axon, insulated with the myelin sheath. This electric signal triggers the release of chemicals.

At a synapse, the plasma membrane of the presynaptic neuron comes into close contact with the membrane of the target (postsynaptic) cell (see Figure 1). At a chemical synapse, the synaptic vesicles which contain neurotransmitters merge with the cell membrane of the postsynaptic cleft, releasing neurotransmitter molecules into the small space (the synaptic cleft) that is adjacent to another neuron. These molecules then bind to the receptors which have a complementary shape to them, on the receiving cell's side of the synaptic cleft. Release of neurotransmitters usually follows arrival of an action potential at the synapse. Finally, the neurotransmitters must be cleared out of the synapse efficiently so that the synapse can be ready to function again as soon as possible.
There are several types of neurotransmitters. They are classified into amino acids, peptides and monoamines. The two main types of amino acid neurotransmitters are Glutamate and GABA. By far the most prevalent transmitter is glutamate, which is excitatory at more than 90% of the synapses in the human brain. The next most prevalent is GABA, which is inhibitory at more than 90% of the synapses that do not use glutamate.

Glutamate is used at the great majority of fast excitatory synapses in the brain and spinal cord. Nerve impulses trigger release of glutamate from the pre-synaptic cell. In the opposing post-synaptic cell, glutamate receptors bind glutamate and are activated. Glutamate is involved in cognitive functions like learning and memory in the brain. This is to do with a form of synaptic plasticity known as long-term potentiation (LTP). In Fig. 2, a synapse is repeatedly stimulated by neurotransmitters passing between the synapse. In Fig. 3, it shows that this causes the post-synaptic cell to form more receptors. This in turn causes release of more neurotransmitters (Fig. 4), which means that the end result is a stronger link between neurons (Fig. 5). The more receptor sites, the more two neurons are bound to each other, and the more effective memory and learning. This is why glutamate is essential to learning and functions.

GABA (gamma-Aminobutyric acid) is used at most of the fast inhibitory synapses in virtually every part of the brain. GABA stops action potential which glutamate starts or maintains. Many sedative/tranquilizing drugs act by enhancing the effects of GABA.
As you can see from Fig. 6 below, GABA and Glutamate have opposing effects. You can also see the drugs that increase glutamate activity such as caffeine and PCP, also decrease GABA activity and vice versa (9).

The research would suggest that if we can raise the levels of glutamate in our body, it should help us improve our cognitive abilities. However, increasing the levels of glutamate can have negative effects. If you increase the levels of glutamate, with similar number of receptors on the post-synaptic cell for the glutamate to bind to, it can cause excess glutamate to deposit outside the neuron. This then causes calcium ions to enter cells via special protein channels, leading to neuronal damage and eventual cell death. This is called excitotoxicity. The mechanisms of cell death include damage to mitochondria from excessively high amounts of Ca2+ in the cells (10).

Another way to potentially increase learning is as mentioned above, by increasing the number of receptors between the two neurons. The creation of more receptors and even neurons is mediated by the brain-derived neurotrophic factor (BDNF). BDNF acts on certain neurons of the central nervous system and the peripheral nervous system, helping to support the survival of existing neurons, and encourage the growth and differentiation of new neurons and synapses (11).

Even though most of the neurons in the brain are formed prenatally, parts of the adult brain still retain the ability to grow new neuron from neural stem cells, in a process known as neurogenesis. Neurotrophins are chemicals that help to stimulate and control neurogenesis, with BDNF being the most active of those ‘family’ of chemicals. BDNF is present in high concentration in hippocampus and cerebral cortex (12).

So we can say that BDNF makes glutamate more effective as BDNF causes the creation of more receptors which means there are more receptors for the glutamate to bind to, hence increasing the ability to learn and memorise. However, what causes the release of BDNF?

Studies show that surges of BDNF are released by exercise. A study conducted by Carl Cotman (2011) at Columbia University, mice were divided into four that ran for zero, two, four or seven nights, and were then injected with a molecule that binds to BDNF so that levels of the protein could be measured. The mice that exercised showed higher levels of BDNF and also there was a direct relationship between the amount of running that the mice did and
BDNF levels in their brains. Moreover, the elevated levels of BDNF were not just found in areas of the brain associated with movement, but in the hippocampus as well, a brain area strongly associated with learning and new memory formation\(^{(13)}\).

In a 2007 German study, researchers had participants go through bouts of intense exercise, which was then followed by a vocabulary learning task. Results showed the predicted spike in BDNF levels in the exercise group, but also that the exercise group learned new vocabulary 20 percent faster than the control group\(^{(14)}\).

The above studies would support that exercise results in an increased level of BDNF, which then corresponds to a better ability to learn and memorise. The reason why the brain loses the ability to recall as it ages is because the neurons present lose some of the mitochondria present. Mitochondria are the site of respiration in cells, a process in which oxygen and glucose are converted to produce molecules of ATP which the neuron can use to carry out other processes fast and effectively.

However another study carried out by Mark Davis at the University of South Carolina, which was published in the Journal of Applied Physiology, showed that the levels of BDNF in the brain of mice increased after half an hour a day of treadmill running. The mice's brain cells also had more mitochondrial DNA, which suggested that exercise stimulated production of mitochondria in the brain as well. Davis concluded that BDNF released, causes changes by bringing more of ‘these power-houses’ online, which increases the energy supply, allowing the brain to work faster and more efficiently\(^{(15)}\).

**Relevance to Medicine**

The link between BDNF and learning to age-related illnesses is quite a large one. Age-related illnesses such as Alzheimer’s are caused by extreme reduction in the hippocampus and cerebral cortex of the patient (see Figure 7)\(^{(16)}\). This means that their ability to recall information is reduced, and in advanced stages the patient may go into a vegetative state, as they lose their ability to perform even the most simple of tasks.

![Figure 7 - Comparison of a normal brain (left) with a brain of person with Alzheimer’s (right)](image)
As BDNF is present in high concentrations in the hippocampus and the cerebral cortex, shrinkage of both those areas, as a result of Alzheimer’s, means that levels of BDNF secreted by the brain are significantly lowered. This essentially means that cognitive ability such as learning and memorising is significantly reduced.

Another medical relevance of BDNF is to do with depression. Release of the stress hormone corticosterone has been shown to decrease the amount of BDNF present in rats. This has also lead to an eventual atrophy of the hippocampus. Supporting this, glutamate, exercise, antidepressants and other various treatments for depression has shown to increase the expression of BDNF in the brain. As both the Alzheimer’s disease and depression lead to atrophy of the hippocampus, there must be a link between levels of BDNF and those two diseases (17).

DISCUSSION

As I have explained above, the key to learning is to increase amount of BDNF present. Studies have shown how BDNF produced naturally with exercise has a positive effect on the brain. BDNF itself is a protein encoded by the BDNF gene, and composed of amino acids. If the primary structure of BDNF can be replicated, then the protein could be artificially synthesised and could be sold as a drug or a supplement.

Proteins have a polymer like structure and all are composed of amino acids, which act as monomers. All amino acids have the same structure, except the R- group as shown in the figure, which differs (see Figure 8). There are 20 types of amino acid that are present, and so there are 20 types of R-groups that can potentially be synthesised. Amino acids join together in a condensation reaction and they form a peptide bond between the nitrogen in the amine group and the carbon in the carboxyl group, on adjacent amino acids (see Figure 9). The different sequence of amino acids results in a different tertiary structure of the protein. So in order to artificially synthesize BDNF, scientists will have to replicate the primary structure of the protein (18).

This drug could be a future cure for Alzheimer’s disease as the drug would cause an increase in the low BDNF levels in the hippocampus, thus increasing the ability of the person to recall and learn new information.

Another natural way of increasing the amount of BDNF present in the drug is caffeinated drink such as coffee. Coffee is found to have increased the levels of BDNF and glutamate present and so having a set amount of caffeine could increase the natural production of BDNF in the body. A study was carried out to find out the association between coffee and/or tea consumption at
midlife and risk of dementia/Alzheimer's disease (AD) in later life. After an average follow-up of the participants of 21 years, 1409 individuals (71%) aged 65 to 79 completed the re-examination in 1998. A total of 61 cases were identified as demented (48 with AD). Coffee drinkers at midlife had lower risk of dementia and AD later in life compared with those drinking little coffee. The lowest risk (65% decreased) was found in people who drank 3-5 cups per day. Tea drinking was relatively uncommon and was not associated with dementia. This would suggest that coffee drinking at midlife is associated with a decreased risk of dementia later in life (19).

Moreover, another cause of Alzheimer’s disease is hypothesized to be because of reduced synthesis of the neurotransmitter acetylcholine. Acetylcholine is an excitatory neurotransmitter at neuromuscular junctions in skeletal muscle. The low levels of acetylcholine are often contributed to the action of the enzyme acetylcholinesterase which breaks down the neurotransmitter, acetylcholine (20). Most of the drugs that are used to treat Alzheimer’s disease are chemicals which inhibit this enzyme, and so the resulting accumulation of acetylcholine causes continuous stimulation of the muscles, glands, and central nervous system. Drugs such as Donepezil and Galantamine are examples of two drugs used to treat Alzheimer’s disease by inhibiting the enzyme that breaks down acetylcholine (21).

Medical cannabis is also another way of potentially curing Alzheimer’s disease (22). Medical cannabis contains the substance THC (tetrahydrocannabinol) which is inhibits the enzyme acetylcholinesterase in a much more effective way than other drugs on the market. This could be a cheaper substitute to using drugs such as Donepezil or Galantamine, as THC is a much easier substance to synthesize. In the cannabis plant, THC occurs as THCA (tetrahydrocannabinolic acid). Over time, or when heated, THCA is decarboxylated - a chemical reaction occurs removing the carboxyl group present in THCA and releases CO2 - producing THC (23).

Contemplating the evidence above, the new drug developed to potentially cure Alzheimer’s could contain BDNF (artificially synthesized), THC (or an alternative acetylcholinesterase inhibitor) and small amounts of caffeine which would all play their individual role combatting against Alzheimer’s disease.

The current studies on the link between BDNF and increased ability to learn aren’t clear. A way of improving this could be by carrying out a series of controlled experiments using embryonic stem cells.

It is needless to say prevention is better than cure and one of the way of preventing Alzheimer’s disease could be through GPs being able to prescribe exercise. This could be especially relevant for those patients that have a family history of Alzheimer’s disease. My proposed idea would be that for patients that do have a family history of Alzheimer’s, after the age of 60 they should be prescribed set hours of exercise weekly, and this should be accompanied by a free gym membership to encourage them to exercise, increase their BDNF production and help stave off dementia.

This research into the role of the BDNF in improving learning could also be crucial for the younger generation. If the research does prove that increased levels of BDNF can significantly improve learning, it could mean better exam results in general for the youths. Further research
could be carried out to prove whether exercise does improve learning or not. A way this research could be carried out is by analysing results of students with similar results but then getting a group of those students to carry out vigorous exercise weekly for a year and the other control group to carry out minimal exercise. If BDNF and learning are linked, the research would suggest that the group that carried out vigorous exercise achieved better grades on average than the group of students who carried out minimal exercise. If the test is positive, i.e. the results conclude that exercise has a direct link to improved exam performance because of the role of the BDNF, and then this could lead to the national curriculum being revised with more hours of weekly P.E lessons being imposed upon students.

Ethical issues

There are several ethical issues that arise from carrying out embryonic stem cell research to improve on current research whether BDNF and ability to learn are closely related or not.

One of the ethical issues is that some people argue that the embryo has full moral status from fertilisation onwards. People claim that the embryo has the potential to be a person and so should have all the obligatory rights a human should have. The arguments against this view are that an early embryo hasn’t developed yet and so it doesn’t have the psychological, physical or emotional characteristics we would associate with a human. At this stage, the embryo is merely a ball of cells. People who argue against this point claim that even though something might have the potential to become a human, it shouldn’t have the same rights as a human.

Another ethical issue concerning embryonic stem cell research is the 14 day cut-off point after fertilisation. After the 14 days, people argue that the embryo has developed a central nervous system and therefore has senses, and so in theory would be able to feel pain. People argue that if we are allowed to take organs from patients that have passed away and have lost all senses, then surely using embryos with no central nervous system should also be allowed. Moreover, after the 14 day cut-off point, the embryo has developed sufficiently that at that point is no longer able to split to form twins. However, stem cell research will be slightly harder to carry out on embryo’s that have barely developed which is the reverse side of the argument.

Another ethical issue is whether the embryo should be given increasing status as it develops. Many people are for this view as they feel there are separate stages in the development of the embryo for example, the embryo at a few days after fertilisation when it is merely a ball of a few cells should have much less status then when the embryo significantly divides to a foetus. However, arguments against this view are that we protect a person’s life and interests not because they are valuable from the point of view of the universe, but because they are important to the person concerned. Whatever moral status the human embryo has for us, the life that it lives has a value to the embryo itself. Also, if we judge the moral status of the embryo from its age, then we are making arbitrary decisions about who is human. For example, even if we say formation of the nervous system marks the start of personhood, we still would not say a patient who has lost nerve cells in a stroke has become less human.

Moreover, another ethical issue about the future developments of the drug I have proposed could arise from initial testing of the drug on animals. People against testing the drug on animals would advocate that an animal has its own rights, and they are not ours to do as we please. Many religious views also state that we have a moral obligation to animals not to cause
them any pain or discomfort. People will argue that the drug could be tested using alternative methods such as testing on human volunteers. Another argument against animal testing is that animals differ in anatomy to humans quite significantly. The results of the drug may not be the same in animals as they are in humans. The drug containing BDNF might increase the hippocampus in lab rats; however, when given to humans might cause undesirable side-effects (25).

However, people do argue for the use of animal testing where many people deem it necessary to develop a cure for Alzheimer’s, a disease which is so costly to society today. Some say that animals would provide a better medium of testing then even humans and this stems from the fact that the animals tested for the drug will have short life spans, so the effect of the drug could be studied throughout their life span. In humans, if we wanted to know whether the drug would cause problems later in life, the study would have to span across a 20-30 year period.

CONCLUSION

Most aspects of my theoretical drug have already been developed or looked into. A problem that the production of the drug would face would be the artificial synthesis of the protein, BDNF. It is quite a complex protein, and as organic chemistry is quite a unrefined form of chemistry, getting the structure of the protein exactly right will be quite a challenge for chemists. The most likely way to synthesise it into a product would be to build a much larger protein, which when digested would hydrolyse by the action of enzymes, causing some peptide bonds to break, and BDNF to be the end product. This problem could be overcome in the next few years, when technology develops and artificial synthesis of proteins can be done fairly easily.

Moreover, another problem that could arise from the production of this drug is that the level of BDNF in the drug would have to be carefully controlled, as two studies have suggested that increased levels of BDNF have been linked to increased itching in patients that have eczema. In order to prevent this from happening, the drug would have to be carefully trialled and any side-effects would have to carefully monitored, before the drug can be released (26).

Another problem with my theory is that the cause of Alzheimer’s disease is not well known or understood. There have been several theories on the cause of Alzheimer’s such as the Cholinergic hypothesis, the Amyloid hypothesis and the Tau hypothesis. I have based my potential cure for Alzheimer’s on the Cholinergic hypothesis, but the rest have to be considered and further research has to be carried out to find out which hypothesis is the most likely cause of Alzheimer’s (27).

In conclusion, the drug, if produced could benefit society hugely. There will be ethical opposition to research and testing of this new drug but I strongly believe that the advantages will far outweigh the disadvantages as this new drug could drastically improve the life of many people for the better.
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