HOW EXERCISE CAN MAKE THE SYMPTOMS OF NEURODEGENERATIVE DISEASES LESS PRONOUNCED

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DISTINCTION

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Abstract

The aim of this report is to explain how exercise can be utilised as a method of making the symptoms of neurodegenerative diseases which patients experience less pronounced, therefore also changing how exercise is ‘promoted’ to patients.

In Britain over 820,000 people are affected by dementia alone, already suggesting that neuroscience research such as into Brain-Derived Neurotrophic Factor is largely required in helping to save the lives of many as well as improve the quality of life for the many that suffer with a neurodegenerative disease [1].

1. Introduction

1.1 Overview of Neurodegenerative disease

‘Neurodegenerative’ is the term used for degenerative nerve diseases, diseases which are associated with the atrophy of certain parts of either the central or peripheral structures of the nervous system. A neurodegenerative disease is defined as ‘hereditary and sporadic conditions which are characterised by progressive nervous system dysfunction’ [2]. This neurodegeneration involves a gradual loss/death of neurons or nerve cells that are found in your brain which in turn means it becomes difficult for the patient to complete their daily functions as well as before; this is because the neurons are used to transmit information throughout the body and if they are dead then the information that needs communicating to various muscles will not be transmitted.

As seen in figure 1, a neuron uses inputs in the forms of dendrites, and outputs in the forms of axons to communicate information to the brain, muscles and other neurons (via Sensory, Motor and Interneurons respectively); to bridge the synaptic gaps between each neuron, neurotransmitters carrying chemical messengers or electrical impulses are transmitted which cause the whole body to have neuron connections which allows information transmitting to different parts of the body. Due to the fact that neurons are highly specialised nerve cells and form an interconnected web around the body, the degeneration of neurons can result in terminal diseases which currently have no cure. Moreover, variation in the major types of neurotransmitter could lead to potential disorders as well [4].

1.2 Types of Neurodegenerative disease

• Alzheimer’s Disease

Alzheimer’s disease is a progressive disease which is the most common cause of dementia, leading to mood swings and the loss of memory as well as problems communicating to others. Approximately 496,000 people are affected by
Alzheimer’s disease specifically in the United Kingdom, with age being the greatest risk factor (one in 14 people over 65 years old and one in six over 80 years old are affected by Alzheimer’s disease) [5]. The direct cause for Alzheimer’s disease has not been discovered yet but the hallmarks have been identified from autopsy results: plaques and tangles, the build-up of proteins in the brain. Plaques are deposits of protein beta-amyloid accumulating in the spaces between neurons whereas tangles are deposits of the protein tau inside the nerve cells. The theory is that these plaques and tangles inhibit communication between the neurons which makes it difficult for them to survive [6]. A shortage of the neurotransmitter Acetylcholine and excess glutamate is also associated with Alzheimer’s disease.

- Huntington’s Disease

Huntington’s disease is a hereditary disease which gets passed down easily through generations due to the disease having the dominant allele. It is caused by the degeneration of the neurons in certain areas of the brain such as the cells of the basal ganglia; within the basal ganglia Huntington’s disease affects the striatum within the caudate nuclei and the pallidum. These structures within the basal ganglia coordinate movement which means that the degeneration of the neurons within this area can lead to symptoms such as uncontrolled movements. Huntington’s disease also affects the outer surface of the brain, the cortex; the cortex controls thought, perception and memory, meaning the symptoms of Huntington’s disease are also the loss of faculties such as intellect and emotional disturbance [7].

- Parkinson’s Disease

Parkinson’s disease occurs when the neurons in the part of the brain which control muscle movement, the substantia nigra, become impaired or die. These neurons normally produce the chemical neurotransmitter dopamine which has the function of transmitting signals from the substantia nigra to the next major neuronal station in the brain, the corpus striatum, which allows fluid and controlled movements in the muscle activity. Therefore logically without enough dopamine there would not be enough connections from the neuron receptor sites in the substantia nigra to reach the effector sites in the muscles to enable purposeful movement, creating the symptoms of Parkinson’s such as trembling limbs, rigidity/stiffness, bradykinesia (slowness of movement) and postural instability (poor balance). The actual cause for why the neurons in the substantia nigra die is still unknown but theories of environmental toxins, genetic predisposition, aging, and oxidative damage are all valid with some supporting evidence as well [8].

- Motor Neurone Disease
Motor Neurone Disease, also known as Amyotrophic Lateral Sclerosis, is when there is a progressive degeneration of the upper and lower motor neurons in the spinal cord, somatic cranial nerve motor nuclei and within the cortex. The causes of it are unknown and it is sporadic (2/100,000 per year are diagnosed with it in its sporadic form) but theories include oxidative neuronal damage, genetic mutations, glutamate mishandling, and abnormalities of neurofilament-mediated axonal transport. Research suggests that the most people contracted with Motor Neurone Disease have a higher level of the neurotransmitter glutamate; excess glutamate may disrupt the chemical communication between the neurons for the nerve cells to function properly. However, other factors such as toxicity of cells (due to the lower production of antioxidants) and formation of aggregates (abnormal protein clumps that develop inside neurons) have all been put forward.

1.3 BDNF production and effects

Brain-Derived Neurotrophic Factor (BDNF) is a protein which mediates the creation of more neuron receptors and stimulates neurogenesis. Neurogenesis is the creation of new neuron connections due to the increased number of receptor sites and the increased number of dendrites which BDNF also stimulates the production of. BDNF also produces more mitochondria in the neurons which allows for more sites where energy in the form of Adenosine Triphosphate (ATP) can be released from aerobic respiration to allow for the active transport and formation of the vesicles of neurotransmitters, as well as to open and close Sodium and Potassium channels in the axons; the more energy there is means the more efficient the transmission and communication of information is. Recently it has been widely publicised by the media that scientists have discovered that after strenuous aerobic exercise there are higher levels of BDNF proteins in the blood; this is significant because it has now been suggested and tested that as BDNF creates more neuron connections and exercise produces BDNF, exercise can be used as a medical ‘treatment’ to relieve the symptoms of some diseases where there is a shortage of neuron receptor sites due to degeneration, and perhaps even where there is a shortage/excess of a certain chemical. BDNF is thought to have been part of the human being’s evolutionary process: hunting for food meant that our brains had to remain sharp and active during this time particularly, so BDNF is thought to have been the body’s ‘reaction’ to this nature (exercising nowadays is similar to hunting in the sense that aerobic respiration through running is required to produce BDNF).

1.4 Current studies

Presently there have been some studies and research conducted by scientists to try and explain what the significance of BDNF production is via exercise and how exactly it can be used to treat people who have been diagnosed with neurodegenerative diseases. For example, to prove that exercise does indeed affect the body’s production of BDNF, an animal study was performed in the Brain Injury Research Centre at the University of California, Los Angeles and then published in the Neuroscience journal, showing that if adult rats were allowed to exercise/run at will for a period of time (in this case one week),
the memory centre of their brains (the hippocampus) contained many more BDNF molecules and precursor molecules soon to develop into BDNF molecules than the memory centres in sedentary rats. This study have been supported by other similar studies, such as one conducted in Brazil on mice where animal memory tests were conducted and the mice which had exercised beforehand had been the most prolifically correct in these tests. Even more recently in the Republic of Ireland the same test was conducted on male humans, where one group would exercise before a memory test and would perform better during the test than the opposing group who did not exercise prior to testing \(^{[11]}\).

All of these studies show that exercise is indeed an important factor in the production of BDNF but scientists have yet to find out why the sudden increase in the Brain-Derived Neurotrophic Factor occurs after exercise.

2. Discussion

- **2.1 Relieving symptoms with BDNF**

As it is now known that there is an increase in BDNF whenever an aerobic exercise is completed, scientists are currently researching how this information can be significant in helping reduce and relieve the symptoms shown by neurodegenerative diseases on patients. As discussed previously, the rise in BDNF would stimulate neurogenesis, the creation of new neurons in the brain, particularly in the hippocampus which in turn could allow more connections between neurons to be thrive and therefore hypothetically memory and learning would improve, as well as other factors which are affected by an increase in connections from muscles to the central nervous system such as purposeful movement. As figure 2 shows, BDNF is an ideal neurotransmitter to benefit from exercise as it can be transmitted retrogradely and anterogradely which means it can have a greater impact in gene transcription and synaptic transmission as well as enhancing neuronal resilience.

**Figure 2**

Figure 2 also shows that an increase in BDNF could benefit the transmission of other neurotransmitters such as glutamate; the BDNF binds to its receptor TrkB presynaptically to modify the transmitter released and also binds to TrkB postsynaptically to modify the postsynaptic sensitivity like interactions with the NMDA receptors for glutamate, which in turn increases the activity of these receptors, meaning more relevant and appropriate communications to other body areas are made.

Using this knowledge, it can be deduced that as excess glutamate is associated with the likes of Alzheimer’s disease and Motor Neurone Disease, producing more receptors for glutamate such as NMDA receptors would lower the excess amount of glutamate which
disrupt chemical communications between the neurons, therefore also drastically reducing
the symptoms of memory loss and inability to learn new subjects easily. Once the
glutamate is in less of an excess, there is more binding due to the increased number of
NMDA receptors and more Gamma-Aminobutyric Acid is released, the chief
neurotransmitter in the vertebrate central nervous system which also ensures that balance is
restored in the body.

The glutamate transporters (Excitatory Amino-Acid Transporters) which regulate the
amount of glutamate in extracellular space by removing excess glutamate and reducing the
uptake of glutamate in the brain get damaged in diseases such as Alzheimer’s disease which
means that the glutamate transporters sometimes work in reverse which causes this excess
 glutamate abundance/accumulation around cells. This process leads to Calcium\(^{2+}\) ions
entering the nerve cells via the NMDA receptors which ends up eventually causing damage
to these neurons which eventually die; this mechanism for nerve cell death is called
excitotoxicity\(^{[13]}\). Hence by ensuring the glutamate transporters do not ‘malfunction’ (by
exercising and producing BDNF) it is less likely that more neurons will die through
excitotoxicity due to the better regulation of the neurotransmitter glutamate, resulting in
less rapid memory loss.

Similarly, in Huntington’s disease, the ability to reduce the symptoms of the disease can be
followed through with exercise and increasing BDNF levels. As well as assisting through
increasing the neuron receptor sites, etc. as mentioned previously to improve memory and
balance of movements, Huntington’s disease has further complications in terms of
significant changes to the patient’s mood. A proposed symptom of Huntington’s disease is
depression which ties in with the mood swings and random irritability, anger and sadness
the person feels. Research suggests that people with Huntington’s disease and general
depression have a significantly lower level of BDNF in their blood plasma\(^{[14]}\). Further
research has also shown that the link of depression to low BDNF is through the
neurotransmitter serotonin which transmits signals regarding mood, anxiety and depression.
It is suggested that BDNF affects the gene for the serotonin transporter called Solute Carrier
Family 6, Member 4 (SLC6A4); the serotonin transporter is a cell membrane protein and
enables ‘serotonin reuptake’ where the serotonin gets transported from the synapse between
two neurons and then back into the original neuron where it came from. Research shows
that the inheritance of some forms of the serotonin transporter has led to some people
carrying mood disorders; these people are considered to be four times more likely to be
diagnosed with clinical depression (which is another symptom possibility for Huntington’s
disease)\(^{[15]}\).

Again similarly in Parkinson’s disease there are low levels of dopamine which result in
tremors starting from the hands and then spreading through the arms to the rest of the body
as well as a slowness of movement. As suggested previously, the lower levels of dopamine
can be rectified by increasing the number of mitochondria in the neuron cells (via exercise
and BDNF production) which would provide more energy for the dopamine to be actively
transported between neurons and through synapses to the rest of the body. It is widely
believed that rolling a ball/object in one’s hand during the early stages of Parkinson’s
disease can make the tremors and shaking less pronounced; this is because as the hand
moves the body’s central nervous system always has to communicate that movement from
the brain to the muscles in the hand via receptors in the neurons and neurotransmitters\(^{[16]}\).
This strengthens the ‘connections’ between the neurons from the brain to the muscle. Likewise with an increase in BDNF levels and neuroplasticity encouraged, these ‘connections’ are strengthened again because of the new pathways developed from the brain to the muscles. This means that exercise will help make the tremors and slow movements insinuated Parkinson’s disease less pronounced as well.

- **2.2 Available symptom treatments and management**

Currently there is no definitive cure for the majority of neurodegenerative diseases and most medicine and drugs used to combat these diseases are trying to relieve the symptoms of the diseases temporarily and ensure the patient has a better quality of life living with the possibly terminal disease.

In idiopathic Parkinson’s disease, the drug therapy does not prevent disease progression, but it improves most patients’ quality of life. Dopaminergic drugs are used to treat Parkinson’s disease, such as Dopamine-receptor agonists, Levodopa, and Monoamine-oxidase-B inhibitors. Levodopa in particular is the most commonly used drug and is the pre-cursor for the neurotransmitters dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline) which means that it differentiates into dopamine (and the other neurotransmitters) when required, increasing overall dopamine levels and relieving some of the slowness and shakiness symptoms of Parkinson’ disease [17]. Antimuscarinic drugs are also used in parkinsonism but are less effective than dopaminergic drugs and are also associated with cognitive impairment (despite reducing tremor and rigidity) [18]. The drugs which are used in essential tremor, chorea, tics and related disorders, including the likes of Huntington’s disease and Motor Neurone Disease, are Tetrabenazine (specifically used to treat the chorea witnessed in Huntington’s disease) and Riluzole (used to manage Motor Neurone Disease and extend the patient’s life). Riluzole for Amyotrophic Lateral Sclerosis blocks the Tetrodotoxin-sensitive Sodium Channels which are normally associated with damaged neurons. This reduces the influx of Calcium ions which indirectly prevents the stimulation of the glutamate receptors [19]. Tetrabenazine acts by depleting the nerve endings of dopamine which means there are fewer ‘random’ dopamine impulses getting transmitted to the muscles which causes the tremors and shaking, overall reducing these symptoms [20].

Alzheimer’s disease and other dementias are treated using Acetylcholinesterase inhibiting drugs. Acetylcholinesterase inhibitors are chemicals which stop the acetylcholinesterase enzyme from breaking down acetylcholine, therefore routinely increasing the level and duration of the actions of the acetylcholine, a neurotransmitter. Acetylcholine is the only neurotransmitter used in motor division in the somatic nervous system (whereas sensory
neurons use glutamate and peptides between their synapses). Donepezil Hydrochloride and Galantamine are examples of reversible inhibitors of acetylcholinesterase [21]. By ensuring there is more acetylcholine there are more pathways between the hippocampus learning centre in the brain and other parts of the brain, making memory loss and the inability to grasp new concepts less pronounced.

These current treatments for these neurodegenerative diseases are quite effective overall in reducing the symptoms of each of the diseases, however it can be possible to prevent the patient ever reaching the stage where such drugs need to be taken. In fact, research suggests that exercise manages to keep the brain healthy because of the added blood flow, where the brain cells take up/use at least 20% of the Oxygen your blood carries, therefore making it more active and preventing the deaths and impairing of neurons within the brain [22]. In this way, neurodegenerative diseases can be prevented, if not totally then, with a greater likelihood, the symptoms would be less pronounced, improving the quality of life of the patient with the disease. Figure 3 shows the amount of blood flow to the various parts of the brain.

- 2.3 Prevention through exercise

As previously stated, rather than exercising as a form of treatment for the disease, using it as a method of prevention could be more beneficial. Already having successful symptom-relieving drugs means although exercising with the disease may still be beneficial, it is not needed as much due to the fact the drugs and medication available can easily make the symptoms less pronounced when a disease has been contracted and are most likely more effective overall at reducing the symptoms because they directly target the method of improvement, unlike exercise which requires the process to occur in stages. For example, dopaminergic drugs take direct action on the dopamine receptors on the neurons and replenishes depleted striatal dopamine, in contrast to exercise which builds more neurons and improves the plasticity of current ones (although this is still helpful as more receptor sites are created, it does not create amino-acid precursors like Levodopa, swiftly acting on replenishing dopamine levels).

Nevertheless, there are some side-effects to each drug used to treat the diseases which include the likes of vomiting, nausea, drowsiness, confusion, hallucinations (in some cases), constipation, temporary anxiety, and more. Blatantly these side-effects are not considered to be pleasant by the patient which is where exercise could come in as a preventative measure against developing such neurodegenerative diseases. On the other hand, the artificial synthesising of BDNF has also been proposed and, despite not being possible in medicine at the moment, it can be a useful and forward-thinking method to help stop neurodegenerative diseases becoming too influential on a person’s life. The injecting of BDNF has already been tested on hamsters but only as an isolated experiment to witness the results, unrelated to degeneration of neurons [24]. By injecting BDNF or swallowing it via tablet form, the patient could have the effects that exercise would bring to the body yet without the need to physically exercise; this would be particularly effective if the patient has a physical disability or is too frail to exercise to create enough BDNF in his/her body. However, as with the negative points of the symptom-relieving drugs available at the
moment, there are bound to be side-effects and damaging or undesirable traits which injecting BDNF as a lone protein would raise, including economic factors which the patient and the doctor have to consider before prescribing the patient the particular ‘BDNF treatment’.

In isolation however, exercise can be a very effective way, with no harmful side-effects or complications, to reduce the symptoms of neurodegenerative diseases and as a method to try prevent the contraction of severe examples as research has shown.

- **2.4 Implementation of exercise as a prevention method**

Although a conclusion can be reached that exercise is beneficial to the brain and can help prevent and treat, to some extent, neurodegenerative diseases, the implementation of such a preventative measure can only be performed from doctor’s themselves if a person is unaware of the overall benefits exercise provides to their body.

When a local General Practitioner was asked about how doctors promote exercise to the general public and to people who had no prior history of any neurodegenerative condition, specifically explaining the benefits it has to the brain, he replied:

“We always explain to the patient that a healthy body equals a healthy mind, but specifically in terms of degenerative brain diseases there is not much you can do if a differential diagnosis appears to suggest that a patient has a neurodegenerative disease. Once a condition is diagnosed, a process of providing early stage medication, if necessary, and educating the patient’s family is initiated, but then if there are further difficulties and the disease develops further then the only options at the moment are drugs to suppress the symptoms and rehabilitation where occupational, physio, and speech and language therapists help the patient to have a better quality of life. Those patients who used to exercise would have a stronger and healthier body physique which would ensure they have a better compliance to the treatment offered, making it more effective [25].”

This interview suggests that although exercise is always a good habit it is not suggested to patients as a measure to prevent or slow down the gradual progression of a neurodegenerative disease, however there are obvious benefits that patients have in future rehabilitation and treatment if they had exercised regularly prior to developing the disease. This allows a new scope for doctors to educate patients regarding how exercise helps the brain in the future and could slightly alter the way doctors educate patients about neurodegenerative diseases in coming years.

**3. Conclusion**

Research into how exercise can affect the brain is beginning to reap results due to the potential capabilities further studies into Brain-Derived Neurotrophic Factor have proposed. With the promise of getting closer to discovering the causes and therefore the absolute cures for neurodegenerative diseases such as Alzheimer’s disease, Huntington’s disease, Parkinson’s disease and Motor Neurone Disease, scientists are further researching how neurogenesis can positively affect the symptoms of these conditions.

However, until then the use of chemicals like BDNF obviously form a route forward for treating patients’ symptoms with certain neurodegenerative diseases, such as trying to stave
off dementia and combating symptoms of mental illness due to aging; the progression of the
disease can be halted using BDNF which in turn means that exercise, the method of
increasing BDNF levels, can also be utilised as a partial preventative method (and even as a
treatment method to increase patient mobility in rehabilitation) for neurodegenerative
diseases. Consequently this advocates that exercise manages to successfully, to an extent,
make the symptoms of neurodegenerative diseases less pronounced.

4. References

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