

The Function of BDNF and Treatment in Neurological Disorder

Yue Dong¹, Kunjie Liu^{2,*} and Yushi Wu^{3,*}

¹Victoria College, University of Toronto, ON M5S 1K7, Toronto, Canada

²B.S. in Biology, College of Saint Mount Vincent, 10471, New York, U.S.A.

³Diablo Valley College, Pleasant Hill, CA 94523, U.S.A.

†These authors contributed equally

Keywords: BDNF, Neurological Disorder, Nervous System Diseases.

Abstract: Brain-derived neurotrophic factor (BDNF) is one of the most well-researched factors that has been shown to regulate mood and stress-coping. There is growing evidence suggesting the dysfunction of the BDNF pathway is likely to cause several types of mental disorders such as Major Depressive Disorders, Stroke, and Parkinson's Disease. This review article provides a detailed examination of the function of BDNF and how it relates to neurological diseases, particularly depression, as well as different studies and theories explaining the mechanism behind how dysfunction of the BDNF relates to depression. The article also discussed different types of treatments, including drug treatment and CRISPR, that target these neurological disorders caused by BDNF dysfunction. Despite the uncertainty in this field, there is still enough evidence suggesting that dysregulation of BDNF can be a risk factor for many neurological disorders. Studies on this topic will likely evoke new perspectives on modern treatments.

1 INTRODUCTION

Neurological disorders range from Major Depressive Disorder (MDD) to stroke, from stroke to Parkinson's Disease (PD), millions of people worldwide are currently estimated to suffer from neurological disorders. This number will be expected to increase significantly in the following years. The only stroke kills more than 6 million people each year, accounting for nearly 11 percent of deaths worldwide. More than 47.5 million people worldwide suffer from dementia, of which AD is the most common cause, while more than 50 million people suffer from epilepsy (WHO 2016). Neuroprotective strategies have been developed to ameliorate brain injury by preserving or restoring neurological function. Brain-derived neurotrophic factor (BDNF) is a widely studied treatment strategy for several neurological diseases. This growth factor plays a significant role in the differentiation, maturation, and survival of neurons. Despite relative success in the laboratory, administering neurotrophic factors has not produced the desired results in clinical trials. Therefore, the neuroscience field will recognize BDNF levels in patients with major depressive disorder (MDD) as a potential threat. The pathway by which low levels of

BDNF directly lead to MDD is not clear right now, but using the hippocampus as a carrier for the relationship between the low level of BDNF and MDD may explain the direct cause-effect relationship. Otherwise, there have been significant advances in SSRIs, MAOIs, and CRISPR technologies to overcome these technical limitations in clinical trials. However, most neurological diseases show not only disorders of BDNF but also damage to its downstream effects-and. Its relevance as a pathological mechanism needs to be emphasized. This review paper attempts to consider and understand the direct and indirect role of BDNF in neurological diseases, the potential pathways between BDNF signaling and depression, as well as the techniques available for clinical trials and the advantages and disadvantages of treatment options. This knowledge provides opportunities and new ideas to guide the design of feasible and effective tools and approaches for treating brain diseases.

2 NEUROLOGICAL DISORDERS

The most significant clinical feature of the decline in BDNF signaling is the occurrence of

neurodegenerative motor disorders. Otherwise, ranging from Major Depressive Disorder (MDD) to Stroke, from Stroke to Parkinson Disease (PD), one of the symptoms of these neurological diseases is the occurrence of neurodegenerative motor disorders to varying degrees. At the same time, BDNF, as an important transmission and balance medium in the brain, has great research value in many clinical and neuroscientific experiments.

2.1 Depression

BDNF has some effects on the development of depression in some ways. Much research has shown that BDNF is closely related to depression, and the presence of BDNF mediates the occurrence of neuronal and synaptic plasticity. In the biological model of stress, BDNF levels were reduced in both the cortex and the hippocampus. In other words, after death, BDNF levels in the brain tissue were significantly lower in those who took antidepressants. In contrast, BDNF expression in the hippocampus was higher in those who did not take antidepressants. Further research suggests that antidepressant-dependent BDNF levels may prevent or reduce hippocampal changes in human samples (Chen 2001). More recently, Cattaneo et al. (2013) demonstrated separation between predictors and targets of antidepressant response. The antidepressant response was associated with changes in the gene BDNF, but the gene did not predict specific changes in physiological indicators of antidepressant and physiological response. As a result, each biomarker needs further study to elucidate its role in predicting antidepressant response. Among the genetic markers, the brain-derived neurotrophic factor (BDNF) gene plays a key role in neurodevelopment and therapeutic response to antidepressants (Ibarguen-Vargas 2009), so antidepressants are associated with increased expression of BDNF in animals brains and human serum (Warner-Schmidt 2006). After the disease becomes chronic, the level of BDNF in the brain is upregulated (Nibuya 1995). Antidepressant therapy results in G-protein-mediated intracellular factor phosphorylation and stimulates BDNF release (Watanabe 2010). Therefore, BDNF secretion and intercellular transport are associated with single nucleotide polymorphisms (SNPS) in the BDNF gene, which leads to valine-to-methionine replacement (Val66Met) (Egan 2003). BDNF expressed as a precursor proBDNF consists of the n-terminal and c-terminal precursors of mature BDNF. The substitution of Val66Met in the anterior domain induces the transfer of secondary structures to replace

the surrounding region (Anastasia 2013). Neurons secrete both the mature BDNF protein and the premitotic domain. Interestingly, compared with the inactive Val66 predomain, secreted predomain containing Met replacement promoted the growth cone retraction of cultured hippocampal neurons (Anastasia 2013). Meanwhile, two recent meta-analyses have shown that Met alleles respond better to antidepressants (Kato 2010). Considering that BDNF mediates the response to antidepressants (D'Sa 2002), polymorphisms modifying BDNF gene expression or different intracellular signaling pathways may play an important role in the treatment and pharmacological response to antidepressants. Therefore, the imbalance BDNF decreasing in the brain may help clarify the relationship between neuroplasticity and the pathophysiology of depression.

2.2 Stroke

Many studies have found that the level of BDNF will decrease with the deterioration of stroke. Otherwise, cerebral dysfunction is common in stroke patients, and BDNF is important for post-stroke recovery. Stroke is the fifth leading cause of death in the United States. Stroke patients often show a decline in neurological function of the brain, accompanied by certain symptoms of movement disorders. A previous study has shown that several therapeutic interventions can enhance functional recovery after stroke, such as exercise and rehabilitation. These treatments lead to beneficial effects of BDNF and brain plasticity, such as improved learning, memory, and motor function and increased expression of related proteins to a certain extent (Ploughman 2005). To date, a clinical study has shown an increase in the number of Treg cells that produce BDNF after stroke, suggesting that Treg cells may be able to deliver BDNF to the site of injury to provide neuroprotection after stroke (Chan 2015). Similarly, strategies to increase BDNF have been widely used in rats with middle cerebral artery occlusion (MCAO).

During stroke rehabilitation, BDNF levels in the nervous system have enhanced the neuroplasticity processes involved in motor relearning. The reduction of BDNF levels in the brain completely negates the recovery of skilled movement (Ploughman 2009). Therefore, the beneficial effects of brain-derived neurotrophic factors in the central nervous system may contribute to post-stroke recovery.

While rapid up-regulation of neurotrophic factor expression in the penumbra has been observed for several days (Madinier 2013), permanent reduction of

BDNF has been observed in animal models of ischemic stroke (Ferrer 2001). However, BDNF has never been measured in the postmortem brain of a stroke patient, although the slight increase in circulating neuronutrient levels observed that stroke might reflect intracerebral levels (Chan 2015). The enhancement of BDNF levels after stroke is mainly associated with peripheral neurons and microglia, which has been considered a brain compensatory mechanism to prevent excessive neuronal death (Bejot 2011, Kokaia 1995). Several studies have concluded that BDNF is not involved in functional recovery after stroke (Zhou 2000). The most likely explanation for this result is that BDNF fails to trigger appropriate neurotrophic signals after stroke due to a pathological imbalance of the TrkB receptor subtype. In fact, TrkB-FL levels declined sharply in the infarct core and penumbra, whereas TRKB-T1 levels were upregulated in human ischemic stroke and ischemic animal models (Hirata 2011). These changes are the result of three separate mechanisms induced by excitotoxicity (Vidaurre 2012).

2.3 PD (Parkinson Disorder)

At the same time, there is increasingly much evidence that the loss of the BDNF signaling pathway or the reduction of BDNF contributes to the pathogenesis of some major diseases and disorders, such as AD and PD (Li 2020). PD is a neurodegenerative disease that can be associated with non-motor symptoms, such as cognitive deficits and changes in BDNF levels. Lack of BDNF signaling is the most common neurodegenerative motor disorder. PD is characterized by progressive loss of dopaminergic neurons in the substantia nigra pars densa (SNpc), coupled with accumulation defects in intracellular α synuclein inclusions (known as Lewy bodies and Lewy neurites). Postmortem studies of PD patients showed that BDNF mRNA and protein were decreased in the susceptible region SNpc and in the striatum receiving neurotrophic support from SN (Parain 1999, Altar 1998). However, the loss of the BDNF survival signal increases the susceptibility of SN dopaminergic neurons to cytotoxic damage and may contribute to the development of PD (Ding 2011, Hung 1996). In fact, inhibition of BDNF expression leads to selective loss of SNpc dopaminergic neurons in older animals and exacerbates motor dysfunction (Boger 2011). In Parkinson's disease, the expression level of BDNF was so low in the neurons that may be facing the biggest risk of injury. It may even trigger an ontology degradation, diseases associated with the intensity and duration, and the severity of the

symptoms of Parkinson's disease (Costa 2015). A study shows even neurodegenerative diseases, if, at a more advanced stage, neurons with low BDNF expression caused irreversible damage (Gyárfás 2010). In recent years, clinical studies have suggested that treatment with anti-Parkinson's drugs may increase BDNF levels (Scalzo 2010). At the same time, exercise therapy can trigger a few plasticity-related events in the brain of PD patients, including cortical motor excitation and changes in BDNF levels (Hirsch 2016). In general, BDNF may be a potential biomarker for assessing cognitive changes in Parkinson's disease and other neurologic syndromes associated with cognitive decline (Costa 2015).

3 MECHANISM BEHIND BDNF PATHWAY

The functional pathway of the BDNF gene is the key to understanding how it relates to numerous different neurological diseases. The BDNF gene is first translated into a precursor proBDNF which is about 32kDa. ProBDNF can undergo an intracellular cleavage by a furin-like convertase to produce mature BDNF (~13kDa) and a BDNF pro-peptide (~17kDa) (Yang 2017). Both proBDNF and mature BDNF (mBDNF) act on hippocampal neuroplasticity by binding to different receptors. While proBDNF preferentially binds to a low-affinity neurotrophin receptor (p75NTR), mBDNF has a higher affinity to a tropomyosin-related kinase B (TrkB) receptor (Castrén 2017). Interestingly, the two receptors show different effects on neural development. The activation of p75NTR by proBDNF promotes apoptosis or neurons, synaptic pruning, as well as NMDAR-dependent long-term depression (LPD) (Lu 2005). However, the binding of TrkB receptors can promote neural survival, synaptogenesis, and neuroplasticity. Many lines of evidence suggest that mBDNF, together with protease plasmin, are highly involved in the late-phase long-term potentiation (L-LTP) in the hippocampus (Lu 2005). Considering its properties and function in neural signalling and development, BDNF has been shown to be related to the pathology of depression and many neurological disorders.

3.1 BDNF and Depression

In 1995, researchers conducted the very first study on the relationship between stress level and BDNF on an animal model, which found that constant stress could significantly reduce the BDNF mRNA level in the hippocampus (Smith 1995). This finding was later tested on depression patients as well. In a study done by Karege and his colleagues, they measured the level of BDNF and neurotrophin-3 in both suicide and non-suicide victims. The result showed that the level of BDNF was significantly low in both hippocampus and ventral prefrontal cortex of suicide victims compared to non-suicide victims (Karege 2004). These studies all suggested that low levels of BDNF could be a potential risk factor for developing depression. Both studies found that the hippocampus was affected also suggested that the hippocampus might be the key link between BDNF and depression.

The pathway of how the low level of BDNF leads to depression is still unclear. However, some theories may be able to explain the mechanism behind it. As mentioned before, mBDNF is crucial to the generation of new synapses and neural development, especially in the hippocampus. A decrease in the mBDNF level can induce less neurogenesis in the hippocampus. This will lead to decreased hippocampal volume and cognitive ability since the hippocampus controls emotions and memory. The study also supported the study, which found patients with depression generally have 4-5% smaller hippocampus than the control group (Yu 2010). Evidence has also shown that the hippocampus plays an important role in regulating the stress-coping mechanism hypothalamic-pituitary-adrenal (HPA) axis and amygdala. Thus, the dysfunction in the hippocampus can lead to difficulties in the stress response (Yu 2010). This could lead to an increase in the risk of major depressive disorder in patients.

Despite the direct interaction with the neuroplasticity, dysfunction in the secretion of mBDNF can also have a deterioration influence on the serotonin pathway in the hippocampus. In the study of Ren-Patterson et al., they conducted an experiment on mice models with double mutant SERT $-/-$ and BDNF $+/-$ genes. The result suggested that the double mutant significantly reduces serotonin in the hippocampus of 37% and hypothalamus of 43% even compared to the single SERT $-/-$ mutant mice. There was also evidence indicating that BDNF plays a crucial role in the differentiation of serotonergic neurons. This all suggests that a low level of BDNF can have deleterious effects on the serotonin pathway. Depression was long known can be improved by

alleviating the level of serotonin in the synapses. This relationship between BDNF and the serotonin pathway also helps to explain how the deficiency in BDNF can be related to depression.

3.2 Polymorphism of Bdnf Gene

Several single-point mutations have been found to be associated with the low level of mBDNF in the brains in the past few years. For instance, plenty of research has been done on a valine to methionine substitution mutation at codon 66, which is likely to cause decreased secretion of mBDNF (Anastasia 2013). According to the study by Anastasia et al. in 2013, BDNF proteins with this mutation have less stable secondary and tertiary structures of the prodomain, which mediate the intracellular trafficking and active secretion of mBDNF. This Val66Met variant decreases the binding efficiency and therefore lowers the amount of mBDNF available in the hippocampus (Anastasia 2013). This theory was also supported by some other studies, which found that patients with the Met66 allele showed abnormal activation in the bilateral hippocampus (Egan 2003). Mice models with this mutation showed similar anxiety behaviors as humans (Bath 2012). Although the mutation was thought to be associated with many mental illnesses such as schizophrenia and bipolar disorder, the strength of this association is still debatable according to current studies (Castrén 2017).

3.3 BDNF and Antidepressants

Right now, multiple different classes of antidepressants have proven to upregulate the release of BDNF. In a study by Nibuya et al. (1995), they found the administration of tranylcypromine increased the level of BDNF mRNA to about 100% in the hippocampus (Nibuya 1995). In fact, many types of serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and even some atypical antidepressants have been shown to alleviate the level of BDNF in brains (Duman 2006). Moreover, chronic treatment of antidepressants can also block the downregulation of BDNF caused by stress (Nibuya 1995). However, not all types of antidepressants have similar effects. For example, there is still some debate over if fluoxetine can alter the expression of BDNF in any part of the brain (Duman 2006). While one search argued that it could increase the level of BDNF in the hippocampus (Dwivedi 2009). Dias et al. suggested that there is no significant difference made by fluoxetine (Duman 2006).

Furthermore, BDNF itself can also have an antidepressant effect on depression patients. In the study done by Shirayama et al., they performed a direct infusion of BDNF in the hippocampus of rat brains and observed a decrease in depressive symptoms. The effect could last as long as 10 days. It is also claimed that such effect was also observed in the treatment with other antidepressants like tricyclic antidepressants (TCA) or SSRIs (Dias 2003). However, this effect has only been tested on rats using different types of behavioral tests such as forced swim test and learned passive avoidance test (Dias 2003). There is no evidence that BDNF will have a similar antidepressant effect on humans, but it suggested a potential path of a new treatment for depression using the BDNF pathway.

4 CURRENT TREATMENT

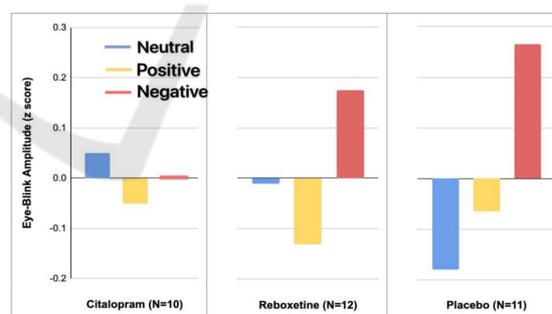
The current treatment of depression is mainly psychological and pharmacological. Antidepressants can have various physiological effects on neuronal, glial, and astrocyte functions and their interactions, which in turn lead to alterations in signaling between neuronal networks, ultimately regulating mood, thinking, and stress response. Currently, there are three main types of pharmacological treatments: SSRIs, MAOIs, and TCAs. In recent years, with the development of CRISPR technology, the groundwork has also been laid for new strategies to treat depression.

4.1 Pharmacology of Antidepressants

4.1.1 SSRIs

Selective serotonin reuptake inhibitors (SSRIs) are usually the drug of choice for depression because they are relatively safe and have fewer side effects than most other types of antidepressants (Shirayama 2002). According to Olfson and Marcus in 2009 (Santarsieri 2015), nearly 67% of people taking antidepressants in the United States were treated with SSRIs. SSRIs work by increasing serotonin levels in the brain. Serotonin is a messenger chemical that transmits signals between nerve cells in the brain and has a beneficial effect on mood, emotion, and sleep. Serotonin is present in the form of vesicles and is transmitted from the presynaptic neuron to the receptor of the postsynaptic neuron via the 5-HT transporter. After transmitting the information, serotonin can be reabsorbed by nerve cells, called "reuptake". Inhibitors of serotonin reuptake trigger

the reactivation of adolescent-like neuroplasticity. By acting on the 5-HT transporter, the SSRI can increase the concentration of 5-hydroxytryptamine in the synaptic gap by inhibiting the reuptake of the neurotransmitter 5-hydroxytryptamine by the synaptic reuptake pump, leaving more serotonin available to transmit further information between nearby nerve cells (Olfson 2009). A 2012 Cambridge University investigation of Short-term SSRI treatment that normalises amygdala hyperactivity in depressed patients also showed that short-term SSRI treatment in depressed patients could remedy amygdala overreaction to negative emotional stimuli prior to clinical improvement in the depressed mood (Cottone 2020). The amygdala is a key center for the fear formation and expression and a key structure for the automatic processing of negative facial expressions. In patients with depression, the organization and function of the amygdala are altered. There is enhanced amygdala activation in processing negative emotional faces in depressed patients, both in conscious and unconscious conditions. The regulation of emotions can be influenced clinically by modulating the function of the amygdala to guide the treatment of related disorders (Godlewska 2012). Indeed, in a behavioral study by Harmer et al. (Zhong 2012), we recently found that a single dose of reboxetine in depressed patients reversed negative emotion bias in facial expression recognition and emotional memory in the absence of any change in subjective mood.



* Values represent mean eye blinks (z transformed) during the presentation of positive, negative, and neutral pictures. There was a significant interaction between group and stimulus type ($F=2.7$, $df=3, 60$, $p=0.04$).

Figure 1. Emotion-Potentiated Eye-Blink Startle Response in 33 Healthy Volunteers After 1 Week of Randomly Assigned Double-Blind Intervention with Citalopram, Reboxetine, or Placebo (Zhong 2012)

4.1.2 MAOIs

MAOIs are one of the most effective antidepressants and have long been used as antidepressants. Although

MAOIs are particularly effective for atypical depression and treatment-resistant depression, MAOIs are not supported as first-line treatments due to safety and tolerability concerns and the need for dietary restrictions (Harmer 2004). By inhibiting monoamine oxidase, MAOIs allow more of these neurotransmitters to be retained in the brain, thereby enhancing mood by improving communication between brain cells. MAOIs are divided into two main categories, non-selective and selective. Non-selective MAOIs inhibit monoamine oxidase A and monoamine oxidase B. As a result, serotonin, norepinephrine, and dopamine levels are increased. They are also known as irreversible MAOIs because they bind irreversibly to the enzymes, permanently blocking their function. Once these enzymes are inhibited, the monoamine neurotransmitters are loaded into preexisting vesicles. This way, when the next action potential reaches the presynaptic membrane, more neurotransmitters are released into the synaptic cleft, thus relieving the symptoms of depression (Tang 2014). In contrast, selective MAO-B inhibitors have a high affinity for DA, phenethylamine, benzylamine and selegiline, pargyline (Thase 2012). Their inhibitory effects are mainly found in the brain's glial cells and can lead to an increase in dopamine (DA) levels in patients.

4.2 CRISPR Technology

4.2.1 The Concept of CRISPR

CRISPR technology is a simple yet powerful genome-editing tool that allows researchers to easily alter DNA sequences and modify gene function, an adaptive immune system used by microorganisms to defend against invading viruses by recording and targeting their DNA sequences. It can be reused in living cells to edit the genomes of mammals and other organisms (Xiao). CRISPR technology was adapted from the natural defense mechanisms of bacteria and archaea (Lander 2016). These organisms use CRISPR-derived RNA and Cas proteins to cut off and destroy the DNA of foreign invaders to thwart attacks by viruses and other foreign agents. CRISPR-Cas9 stands for clusters of regularly spaced short palindromic repeats and CRISPR-associated protein 9. CRISPR is a specialized DNA fragment, and the protein Cas9 is an enzyme that acts like "molecular scissors" that cut two DNA strands at specific locations in the genome and then add or remove DNA fragments. A piece of RNA called guide RNA (gRNA) consists of a small piece of pre-designed RNA sequence (approximately 20 bases long) located

within a longer RNA scaffold (Aparna 2018), designed to find and bind to a specific sequence in DNA. The scaffold partially binds to the DNA, and the RNA bases of the guide RNA are complementary to the bases of the target DNA sequence in the genome to ensure that the Cas9 enzyme cleaves at the correct position in the genome (Aparna 2018). Cas9 follows the guide RNA to the same position in the DNA sequence and cleaves on both DNA strands. In this way, the DNA repair mechanism can be used to alter one or more genes in the genome of the cell of interest, acting more directly on the gene to alleviate depression at a faster rate.

4.2.2 Applications of CRISPR

Although antidepressants are frequently used to treat depression, at least 50% of patients respond that antidepressants do not actually work. Moreover, the clinical response occurs only after weeks to months of treatment and is only effective with long-term adherence to antidepressant therapy (Sander 2014). In recent years, researchers are trying a new approach based on CRISPR technology to alleviate depression in addition to medication. Before the depression, CRISPR technology has been widely used in other fields. For example, in bladder cancer gene therapy, treatment strategies have been ineffective because certain genes, while actively expressed in tumor cells in one organ, may also be expressed at relatively active levels in normal cells in other different tissues. Nowadays, researchers have cleverly used CRISPR gene-editing technology and the principles of logical pathways to solve these problems, providing new ideas for studying tumor gene therapy. Researchers established an editing system for targeted editing of E6 and E7 genes based on CRISPR technology and transfected the system into cervical cancer cell lines infected with HPV-16 positive virus, and experiments with SiHa cells also provide new ideas in the treatment of cervical cancer and other HPV-related cancers as a new therapeutic strategy (Masi 2011).

4.3 New Possible for CRISPR

A study at Pennsylvania State University indicated that enhancing the activity of a subclass of neuronal cells that produce the neurotransmitter gamma-aminobutyric acid (GABA) and elevating GABA neurotransmitter levels had antidepressant effects in mice modeled with depression (Liu 2015). GABA is part of the pathogenesis of anxiety and depression and is responsible for many of the symptoms of these disorders. GABA dysfunction is a major culprit of

depression, and depressed patients often have reduced GABA concentrations in the brain (State 2016). Researchers at Pennsylvania State University increased GABA signaling by disabling GABA receptors in a specific group of neurons suspected of being involved in major depression (Liu 2015). Under normal conditions, this group of neurons, called SST+ interneurons (growth inhibitor positive - GABAergic interneurons), produce GABA, which reduces the activity of other surrounding neurons. In contrast, most peripheral neurons release the neurotransmitter glutamate. When researchers selectively disabled GABA receptors in SST+ interneurons, these cells could no longer receive deceleration signals, so they over-released GABA, which further slowed the glutamate-producing neurons' activity (Liu 2015). As a result, rats receiving this treatment behaved as if they were taking antidepressants in a series of behavioral tests. However, a study by Hyunjung Oh et al. in 2019 showed that GABA was the main determinant, as manipulation of BDNF signaling resulted in an initial deficit in GABA, not glutamate (Oh 2019). The basic anxiolytic-antidepressant representing a GABA-A positive modulator is very promising (Kalueff 2007). The GABA-A type receptor is involved in cell signaling through direct interaction with GABA. There are also two subtypes of GABA-A receptors: one containing the δ subunit δ and the other containing the $\gamma 2$ subunit.

4.3.1 Functional Abnormalities Associated with Mutations

Dr. Steven Mennerick, Professor of Psychiatry at Washington School of Medicine, induced point mutations in the gene encoding the GABA-A δ subunit in the mouse hippocampus using CRISPR-Cas9 technology, making the GABA A δ subunit resistant to picrotoxin resistant, thereby blocking the chloride channel to inhibit receptor activity of the chemical. Mice were then bred with these bitter toxin-resistant GABA-A δ receptors. After dissecting and sectioning the hippocampus of developing mice, they stimulated neuronal cells in the presence of bitter toxins to observe specific responses of δ subunits (Oh 2019). These experiments revealed the contribution of the GABA-A δ subunit to short-term phase synaptic responses after electrical stimulation. Meanwhile, ASDs resulted in a range of emotional and cognitive changes in adult animals, including reduced social interest, increased anxiety-like behavior, and impaired cognitive switch function, accompanied by attenuated mPFC GABAergic

inhibitory synaptic transmission and a significant reduction in the average frequency, but not amplitude, of spontaneous inhibitory postsynaptic current (sIPSC) delivery (CAS 2020). Further testing of GABAergic signaling molecules by the Chinese Academy of Sciences last year revealed that the mRNA expression level of the mPFC GABA synthase GAD65 was also significantly reduced. These suggest that adolescent stress leads to sustained suppression of GABAergic function in this brain region. The decrease in BDNF due to ASDs is mainly associated with reduced levels of BDNF IV promoter transcripts. The results also suggest that mPFC GABAergic synaptic transmission may be a downstream mediating pathway for the depression-like behavioral comorbid cognitive impairment and BDNF signaling impairment caused by ASS. These results suggest that GABAergic synaptic transmission downstream of mPFC BDNF signaling is primarily involved in the onset of depressive comorbid cognitive impairment due to social stress in adolescence, rather than depressive co-morbid anxiety-like behaviors (CAS 2020). This study provides a potential target for future rapid treatment of cognitive dysfunction in depressed patients.

Given that the findings they generated have only been relevant to mice, we must be cautious about interpreting these results. That said, this study will hopefully lay the groundwork for future studies on the role of different cell types and mechanisms, diversifying our approach to the study of depression (Gardner 2018).

5 CONCLUSIONS

BDNF is essential for synaptogenesis, nerve growth, and LTP in the hippocampus and many other parts of the brain. More and more evidence suggest that low levels of BDNF can be a risk factor for neurological diseases like depression, stroke, and Parkinson's disease. In the case of depression, the mutation of Met66Val in the *bdnf* gene can decrease the secretion of mBDNF, which has two possible pathways to alter the function of the brain. Dysfunction of BDNF can cause a decrease in the hippocampal volume and the dysregulation in the serotonin pathway, while both can increase the chance of major depressive disorder in patients. In addition, it was also found that the upregulation of BDNF has an antidepressant effect in depression patients, which leads to new ways to treat this disease. Currently, SSRIs and MAOIs are two of the most common antidepressants available in the markets. Both have shown to be effective in

increasing the level of neurotransmitters such as serotonin and epinephrine, which significantly improve the symptoms of depression but with minor side effects. CRISPR is one of the modern technologies that can potentially treat depression by editing genes such as the *bdnf* gene. There has been an example of researchers introducing a point mutation for the gene of GABA-A δ subunit. With research like this, hopefully, we will be able to treat more neurological diseases using CRISPR in the future.

REFERENCES

- Altar, C.A.; DiStefano, P.S. Neurotrophin trafficking by anterograde transport. *Trends Neurosci.* 1998, 21, 433–437
- Anastasia A, Deinhardt K, Chao MV, Will NE, Irmady K, Lee FS, Hempstead BL, Bracken C (2013) Val66Met polymorphism of BDNF alters prodomain structure to induce neuronal growth cone retraction. *Nat Commun* 4:2490. doi:10.1038/ncomms3490
- Anastasia, A., Deinhardt, K., Chao, M. V., Will, N. E., Irmady, K., Lee, F. S., Hempstead, B. L., & Bracken, C. (2013). Val66Met polymorphism of BDNF alters prodomain structure to induce neuronal growth cone retraction. *Nature Communications*, 4(1). <https://doi.org/10.1038/ncomms3490>
- Aparna Vidyasagar (2018). What Is CRISPR? *Live Science Contributor* April 20, 2018
- Bath, K. G., Chuang, J., Spencer-Segal, J. L., Amso, D., Altemus, M., McEwen, B. S., & Lee, F. S. (2012). Variant Brain-Derived Neurotrophic Factor (Valine66Methionine) Polymorphism Contributes to Developmental and Estrous Stage-Specific Expression of Anxiety-Like Behavior in Female Mice. *Biological Psychiatry*, 72(6), 499–504. <https://doi.org/10.1016/j.biopsych.2012.03.032>
- Bejot, Y.; Prigent-Tessier, A.; Cachia, C.; Giroud, M.; Mossiat, C.; Bertrand, N.; Garnier, P.; Marie, C. Time-dependent contribution of non neuronal cells to BDNF production after ischemic stroke in rats. *Neurochem. Int.* 2011, 58, 102–111.
- Boger, H.A.; Mannangatti, P.; Samuvel, D.J.; Saylor, A.J.; Bender, T.S.; McGinty, J.F.; Fortress, A.M.; Zaman, V.; Huang, P.; Middaugh, L.D.; et al. Effects of brain-derived neurotrophic factor on dopaminergic function and motor behavior during aging. *Genes Brain Behav.* 2011, 10, 186–198.
- CAS, Psychology Institute identifies GABAergic synaptic modulation mechanism of adolescent stress-induced depressive co-morbid cognitive impairment, *Chinese Academy of Sciences*, 2020-12-08
- Castrén, E., & Kojima, M. (2017). Brain-derived neurotrophic factor in mood disorders and antidepressant treatments. *Neurobiology of Disease*, 97, 119–126. <https://doi.org/10.1016/j.nbd.2016.07.010>
- Castrén, E., & Kojima, M. (2017). Brain-derived neurotrophic factor in mood disorders and antidepressant treatments. *Neurobiology of Disease*, 97, 119–126. <https://doi.org/10.1016/j.nbd.2016.07.010>
- Chan, A.; Yan, J.; Csurhes, P.; Greer, J.; McCombe, P. “Circulating brain derived neurotrophic factor (BDNF) and frequency of BDNF positive T cells in peripheral blood in human ischemic stroke: effect on outcome,” *Journal of Neuroimmunology*, vol. 286, pp. 42–47, 2015.
- Chan, A.; Yan, J.; Csurhes, P.; Greer, J.; McCombe, P. Circulating brain derived neurotrophic factor (*bdnf*) and frequency of *bdnf* positive T cells in peripheral blood in human ischemic stroke: Effect on outcome. *J. Neuroimmunol.* 2015, 286, 42–47.
- Characteristics of amygdala volume and functional activation in depression.
- Chen, B, Dowlatsahi, D, G. M. MacQueen, J. F. Wang, and L. T. Young, “Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication,” *Biological Psychiatry*, vol. 50, no. 4, pp. 260–265, 2001.
- China Academic Journal Electronic Publishing House, 10.11886/jissn.1007-3256.2014.06.29.
- Chinese Journal of Behavioral Medicine and Brain Science, June 2012, Vol. 21, No. 6
- Costa, A.; Peppe, A.; G. Carlesimo et al. “Brain-derived neurotrophic factor serum levels correlate with cognitive performance in Parkinson’s disease patients with mild cognitive impairment,” *Frontiers in Behavioral Neuroscience*, vol. 9, p. 253, 2015.
- Cottone, John. “A Better Understanding of SSRI Antidepressants.” *Psychology Today*, Sussex Publishers, 18 May 2020.
- D’Sa C, Duman RS (2002) Antidepressants and neuroplasticity. *Bipolar Disord* 4:183–194. doi:10.1034/j.1399-5618.2002.01203.x
- Dias, B. “Differential Regulation of Brain Derived Neurotrophic Factor Transcripts by Antidepressant Treatments in the Adult Rat Brain.” *Neuropharmacology*, vol. 45, no. 4, 2003, pp. 553–563., doi:10.1016/s0028-3908(03)00198-9.
- Ding, Y.X.; Xia, Y.; Jiao, X.Y.; Duan, L.; Yu, J.; Wang, X.; Chen, L.W. The TrkB-positive dopaminergic neurons are less sensitive to MPTP insult in the substantia nigra of adult C57/BL mice. *Neurochem. Res.* 2011, 36, 1759–1766.
- Duman, Ronald S., and Lisa M. Monteggia. “A Neurotrophic Model for Stress-Related Mood Disorders.” *Biological Psychiatry*, vol. 59, no. 12, 2006, pp. 1116–1127., doi:10.1016/j.biopsych.2006.02.013
- Dwivedi, Yogesh. “Brain-Derived Neurotrophic Factor: Role in Depression and Suicide.” *Neuropsychiatric Disease and Treatment*, 2009, p. 433., doi:10.2147/ndt.s5700.
- Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B,

- Goldman D, Dean M, Lu B, Weinberger DR (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 112(2):257–269. doi:10.1016/S0092-8674(03)00035-7
- Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., & Weinberger, D. R. (2003). The BDNF val66met Polymorphism Affects Activity-Dependent Secretion of BDNF and Human Memory and Hippocampal Function. *Cell*, 112(2), 257–269. [https://doi.org/10.1016/s0092-8674\(03\)00035-7](https://doi.org/10.1016/s0092-8674(03)00035-7)
- Ferrer, I.; Krupinski, J.; Goutan, E.; Marti, E.; Ambrosio, S.; Arenas, E. Brain-derived neurotrophic factor reduces cortical cell death by ischemia after middle cerebral artery occlusion in the rat. *Acta Neuropathol.* 2001, 101, 229–238.
- GABAergic neurons may be a new target for antidepressants. *BioDiscovery*, 2016-11-10
- Gardner, Heidi. (2018) Fighting Depression with CRISPR. *CRISPR NEWS*
- Godlewska, B. R., Norbury, R., Selvaraj, S., Cowen, P. J., & Harmer, C. J. (2012). Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. *Psychological medicine*, 42(12), 2609–2617.
- Gyárfás, T.; Knuuttila, J.; Lindholm P.; Rantamäki, T.; Castrén, E. “Regulation of brain-derived neurotrophic factor (BDNF) and cerebral dopamine neurotrophic factor (CDNF) by anti-parkinsonian drug therapy in vivo,” *Cellular and Molecular Neurobiology*, vol. 30, no. 3, pp. 361–368, 2010.
- Harmer, C. J., Shelley, N. C., Cowen, P. J., & Goodwin, G. M. (2004).
- Hirata, K.; Kuge, Y.; Yokota, C.; Harada, A.; Kokame, K.; Inoue, H.; Kawashima, H.; Hanzawa, H.; Shono, Y.; Saji, H.; et al. Gene and protein analysis of brain derived neurotrophic factor expression in relation to neurological recovery induced by an enriched environment in a rat stroke model. *Neurosci. Lett.* 2011, 495, 210–215.
- Hirsch, M. A.; Iyer, S. S.; Sanjak M. “Exercise-induced neuroplasticity in human Parkinson’s disease: what is the evidence telling us?,” *Parkinsonism & Related Disorders*, vol. 22, Suppl 1, pp. S78–S81, 2016.
- Hung, H.C.; Lee, E.H. The mesolimbic dopaminergic pathway is more resistant than the nigrostriatal dopaminergic pathway to MPTP and MPP+ toxicity: Role of BDNF gene expression. *Brain Res. Mol. Brain Res.* 1996, 41, 14–26.
- Ibarguen-Vargas Y, Surget A, Voure’h P, Leman S, Andres CR, Gardier AM, Belzung C (2009) Deficit in BDNF does not increase vulnerability to stress but dampens antidepressant-like effects in the unpredictable chronic mild stress. *Behav Brain Res* 202:245–251. doi: 10.1016/j.bbr.2009.03.040
- Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *The American journal of psychiatry*, 161(7), 1256–1263.
- Kalueff, A. V., & Nutt, D. J. (2007). Role of GABA in anxiety and depression. *Depression and anxiety*, 24(7), 495–517.
- Karege, Félicien, et al. “Neurotrophin Levels in Postmortem Brains of Suicide Victims and the Effects of Antemortem Diagnosis and Psychotropic Drugs.” *Molecular Brain Research*, vol. 136, no. 1-2, 2005, pp. 29–37., doi:10.1016/j.molbrainres.2004.12.020.
- Kato M, Serretti A (2010) Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. *Mol Psychiatry* 15:473–500. doi:10.1038/mp.2008.116
- Kokaia, Z.; Zhao, Q.; Kokaia, M.; Elmer, E.; Metsis, M.; Smith, M.L.; Siesjo, B.K.; Lindvall, O. Regulation of brain-derived neurotrophic factor gene expression after transient middle cerebral artery occlusion with and without brain damage. *Exp. Neurol.* 1995, 136, 73–88.
- Lander E. S. (2016). The Heroes of CRISPR. *Cell*, 164(1-2), 18–28.
- Li, Xia, et al. “Applications of Acupuncture Therapy in Modulating the Plasticity of Neurodegenerative Disease and Depression: Do MicroRNA and Neurotrophin BDNF Shed Light on the Underlying Mechanism?” *Neural Plasticity*, Sept. 2020, pp. 1–17. EBSCOhost, doi:10.1155/2020/8850653.
- Liu, C., Li, Z., & Zhang, Y. (2015). *Zhongguo fei ai za zhi* = Chinese journal of lung cancer, 18(9), 571–579.
- Lu, B., Pang, P. T., & Woo, N. H. (2005). The yin and yang of neurotrophin action. *Nature Reviews Neuroscience*, 6(8), 603–614. <https://doi.org/10.1038/nrn1726>
- M. Ploughman, V. Windle, C. L. MacLellan, N. White, J. J. Dore, and D. Corbett, “Brain-derived neurotrophic factor contributes to recovery of skilled reaching after focal ischemia in rats,” *Stroke*, vol. 40, no. 4, pp. 1490–1495, 2009.
- Madinier, A.; Bertrand, N.; Rodier, M.; Quirie, A.; Mossiat, C.; Prigent-Tessier, A.; Marie, C.; Garnier, P. Ipsilateral versus contralateral spontaneous post-stroke neuroplastic changes: Involvement of BDNF? *Neuroscience* 2013, 231, 169–181.
- Masi, G., & Brovedani, P. (2011). The hippocampus, neurotrophic factors and depression: possible implications for the pharmacotherapy of depression. *CNS drugs*, 25(11), 913–931.
- Nibuya M, Morinobu S, Duman RS (1995) Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J Neurosci* 15:7539–7547
- Nibuya, M, et al. “Regulation of BDNF and TrkB MRNA in Rat Brain by Chronic Electroconvulsive Seizure and Antidepressant Drug Treatments.” *The Journal of Neuroscience*, vol. 15, no. 11, 1995, pp. 7539–7547., doi:10.1523/jneurosci.15-11-07539.1995.
- Oh, H., Piantadosi, S. C., Rocco, B. R., Lewis, D. A., Watkins, S. C., & Sibille, E. (2019). The Role of Dendritic Brain-Derived Neurotrophic Factor Transcripts on Altered Inhibitory Circuitry in Depression. *Biological psychiatry*, 85(6), 517–526.
- Olfson, M., & Marcus, S. C. (2009). National patterns in antidepressant medication treatment. *Archives of general psychiatry*, 66(8), 848–856.

- Parain, K.; Murer, M.G.; Yan, Q.; Faucheux, B.; Agid, Y.; Hirsch, E.; Raisman-Vozari, R. Reduced expression of brain-derived neurotrophic factor protein in Parkinson's disease substantia nigra. *Neuroreport* 1999, 10, 557–561.
- Ploughman M., Granter-Button S., Chernenko G., Tucker B. A., Mearow K. M., and Corbett D., "Endurance exercise regimens induce differential effects on brain-derived neurotrophic factor, synapsin-I and insulin-like growth factor I after focal ischemia," *Neuroscience*, vol. 136, no. 4, pp. 991–1001, 2005.
- Sander, J. D., & Joung, J. K. (2014). CRISPR-Cas systems for editing, regulating and targeting genomes. *Nature biotechnology*, 32(4), 347–355.
- Santarsieri, D., & Schwartz, T. L. (2015). Antidepressant efficacy and side-effect burden: a quick guide for clinicians. *Drugs in context*, 4, 212290.
- Scalzo, P.; Kümmer, A.; Bretas, T. L.; Cardoso, F.; Teixeira, A. L. "Serum levels of brain-derived neurotrophic factor correlate with motor impairment in Parkinson's disease," *Journal of Neurology*, vol. 257, no. 4, pp. 540–545, 2010.
- Shirayama, Yukihiko, et al. "Brain-Derived Neurotrophic Factor Produces Antidepressant Effects in Behavioral Models of Depression." *The Journal of Neuroscience*, vol. 22, no. 8, 2002, pp. 3251–3261., doi:10.1523/jneurosci.22-08-03251.2002.
- Smith, MA, et al. "Stress and Glucocorticoids Affect the Expression of Brain-Derived Neurotrophic Factor and Neurotrophin-3 MRNAs in the Hippocampus." *The Journal of Neuroscience*, vol. 15, no. 3, 1995, pp. 1768–1777., doi:10.1523/jneurosci.15-03-01768.1995.
- State, Penn. Increasing the activity of the neurotransmitter GABA in the brains of depressed mice has antidepressant effects. *Molecular Psychiatry*, November 8, 2016.
- Tang, Zhuojun (2014). *Advances in antidepressant research*.
- Thase M. E. (2012). MAOIs and depression treatment guidelines. *The Journal of clinical psychiatry*, 73(7), e24.
- Vidaurre, O.G.; Gascon, S.; Deogracias, R.; Sobrado, M.; Cuadrado, E.; Montaner, J.; Rodriguez-Pena, A.; Diaz-Guerra, M. Imbalance of neurotrophin receptor isoforms TrkB-FL/TrkB-T1 induces neuronal death in excitotoxicity. *Cell. Death Dis.* 2012, 3, e256.
- Warner-Schmidt JL, Duman RS (2006) Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. *Hippocampus* 16(3):239–249. doi:10.1002/hipo.20156
- Watanabe K, Hashimoto E, Ukai W, Ishii T, Yoshinaga T, Ono T, Tateno M, Watanabe I, Shirasaka T, Saito S, Saito T (2010) Effect of antidepressants on brain-derived neurotrophic factor (BDNF) release from platelets in the rats. *Prog Neuropsychopharmacol Biol Psychiatry* 34(8):1450–1454. doi:10.1016/j.pnpbp.2010.07.036
- WHO (2016) ; [http://www.who.int/features/qa/55/en/]
- Xiao, Yifan, Ling, Justin, Aranda, Alex, Nixon-Shapiro, Elizabeth, Vasiljević, Filip Monoamine oxidase inhibitors
- Yang, B., Ren, Q., Zhang, J.-c, Chen, Q.-X., & Hashimoto, K. (2017). Altered expression of BDNF, BDNF pro-peptide and their precursor proBDNF in brain and liver tissues from psychiatric disorders: rethinking the brain–liver axis. *Translational Psychiatry*, 7(5). <https://doi.org/10.1038/tp.2017.95>
- Yu, H., & Chen, Z.-yu. (2010). The role of BDNF in depression on the basis of its location in the neural circuitry. *Acta Pharmacologica Sinica*, 32(1), 3–11. <https://doi.org/10.1038/aps.2010.184>
- Zhao, L.R.; Mattsson, B.; Johansson, B.B. Environmental influence on brain-derived neurotrophic factor messenger RNA expression after middle cerebral artery occlusion in spontaneously hypertensive rats. *Neuroscience* 2000, 97, 177–184.
- Zhong, Mingtian, Yi, Jinyao, Zhu, Xiongzhaohao, Yao, Shujiao (2012)