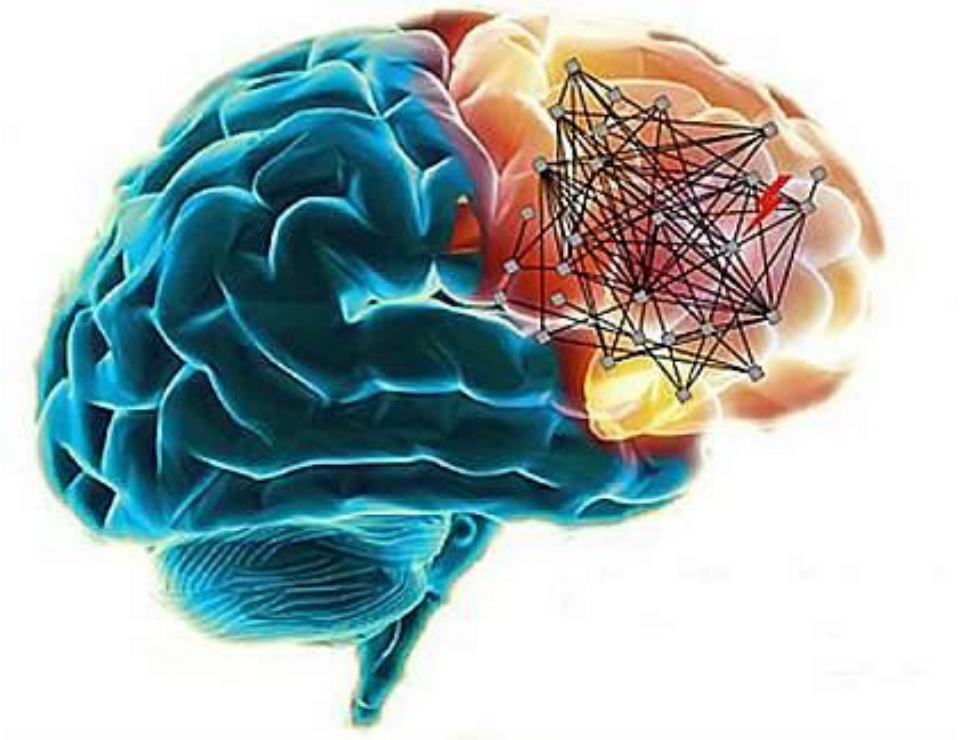
The role of BDNF in the development of schizophrenia



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Abstract

Schizophrenia is a mental and psychotic disorder characterized by hallucinations, hearing voices, and a lack in social functioning. The disease occurs mostly as a relapsing condition and often leads to neurocognitive decline. No clear cause has been found for schizophrenia, though it is known that the disease is multifactorial. The combination of these factors leads to abnormalities in dopamine regulation and reduced crosstalk with other factors such as brain derived neurotrophic factor (BDNF). Being a neurotrophin, BDNF is responsible for many processes in the healthy brain, such as neurogenesis and facilitating synaptic plasticity. A decrease in BDNF is often found in patients with schizophrenia, raising the question whether BDNF is involved in the development of schizophrenia. Therefore, in this review, a detailed overview is provided of the functions of BDNF in healthy tissue. Further, the dysregulation of BDNF in schizophrenia is evaluated and the effect of this dysregulation on neuronal tissue is assessed. Finally, the mechanism of action and effects of some antipsychotic drugs on BDNF signaling are explained and other possible treatment options are examined.

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1. Introduction

The Global Burden of Diseases, Injuries and Risk Factors Study has shown an increase in mental health disorders from 1990 to 2017 (James et al., 2018). These mental disorders emerge during childhood and continually transform into more serious disorders, such as schizophrenia (James et al., 2018). Schizophrenia is a mental and psychotic disorder characterized by positive and negative symptoms. Positive symptoms are also called First Rank Symptoms (FRS). They include symptoms usually not experienced in healthy individuals, like hallucinations and hearing voices (Soares-Weiser et al., 2015). Negative symptoms refer to an absence of normal behaviors. Examples are a lack of motivation, communication or social functioning (Correll & Schooler, 2020). FRS are incorporated in the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV). A diagnosis of schizophrenia is made when an individual shows symptoms indicated by the DSM-IV for several months. After an official diagnosis people may be treated with antipsychotic medications, therapy or alternative treatment methods (Soares-Weiser et al., 2015).

Schizophrenia occurs as a single episode or as a relapsing condition, including 4 main stages. Stages of schizophrenia are characterized in increasing severity of clinical features, ranging from psychosis in stage one to neurocognitive decline in stage four (Fountoulakis et al., 2019). A single episode occurs in three phases: the prodromal, active (or psychotic), and residual phase (Eske, 2021). These phases are also shown in figure 1.

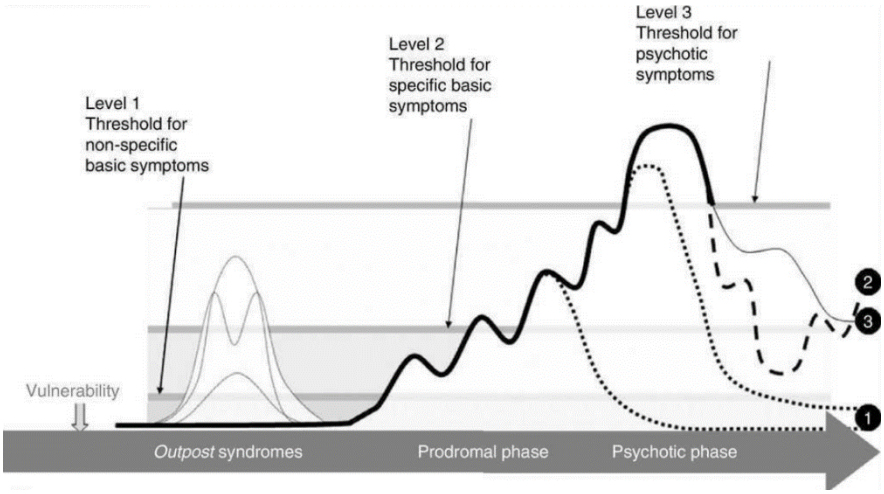

Figure 1: Model of Huber's concept of basic symptoms. The phases of a psychotic episode are shown ending in a (1) reversible post-psychotic basic state, a (2) prodrome of a relapse, and (3) irreversible post-psychotic-basic state. (Miret et al., 2016)

Although the disease progresses differently in individuals, a recent study has shown two distinct subtypes with different neuroanatomical axes (See figure 2). The first subtype shows a pattern of decreased grey matter volume mainly in the thalamus and the medial, temporal, and frontal lobe. These regions are responsible for memory, decision making and processing of auditory information (Karlsgodt et al., 2010). The second subtype however shows a larger volume of grey matter in the basal ganglia, responsible for motor control, emotions and behaviors (Chand et al., 2020). As a result of such abnormal morphology of the brain, patterns of cognitive impairment are often found in individuals with schizophrenia. Impairments may include lower IQ scores and deficits in memory (Wells et al., 2020). In general, studies have shown a hypothesis of accelerated aging in schizophrenia patients.

Indeed, the brain structure of schizophrenic patients appeared to show signs of deterioration, resulting in decreased functional skills and cognitive performance compared to healthy individuals (Huo et al., 2021).

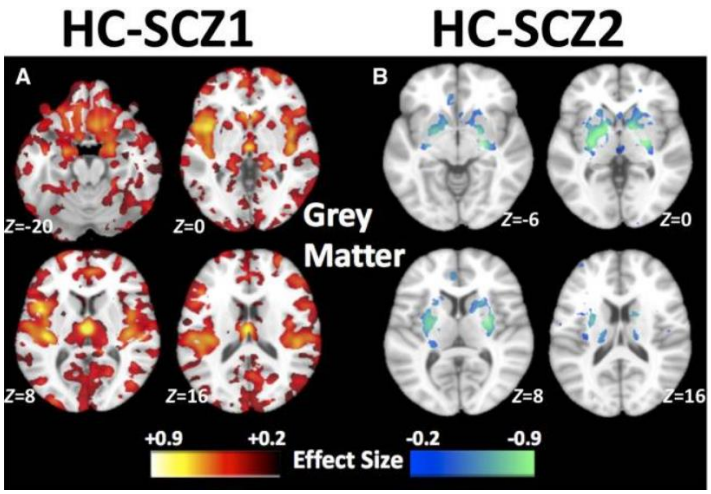

Figure 2: Patterns of grey matter volumes in schizophrenia subtype 1 (SCZ1) and subtype 2 (SCZ2) compared to a healthy control (HC). Colors indicate a significant increase (red, yellow) or decrease (blue, green) in volume. (Chand et al., 2020)

Although no clear cause has been found for schizophrenia, it is known that the disorder is multifactorial. Genetic variations are the biggest risk factor to develop the disease. Genes that are mainly responsible for increasing the risk are neuregulin 1 (NRG1), dysbindin and DISC1, although many other genes have been associated with schizophrenia. Furthermore, drug abuse and environmental factors such as premature birth and viral exposure have been reported to facilitate the development of schizophrenia (Picchioni & Murray, 2007). Other studies suggest that childhood trauma also may be a major factor. The combined factors cause a disruption of brain development and abnormalities in dopamine regulation, that could lead to reduction in dopamine levels in the prefrontal cortex of schizophrenia patients (Slifstein et al., 2015). Dopamine is an important neurotransmitter mediating cognitive processes and it regulates signaling in neurons in combination with other factors such as other neurotransmitters. One such cross-talking factor is brain-derived neurotrophic factor (BDNF) (Morella et al., 2020). BDNF is a neurotrophin that plays a crucial role in survival, differentiation of neurons (di Carlo et al., 2020) and regulation of cognitive behavior (Huo et al., 2021). Deficits in BDNF expression and signaling contribute to the pathogenesis of schizophrenia. Because cognitive deficits are frequently seen due to decreased BDNF signaling, it might be possible that BDNF plays a central role in the development of schizophrenia. Therefore, BDNF might also be a possible target in antipsychotic treatment.

The importance of BDNF in the healthy brain and the protein being a possible target in treatment raise the question: How is BDNF involved in the development of schizophrenia? This thesis aims to provide an overview of the importance of BDNF in patients with schizophrenia. This is done by providing the functions of BDNF in healthy tissue and by explaining the altered expression and signaling of BDNF in patients. Finally, the mechanism of action and the effects of some antipsychotic drugs on BDNF signaling are explained.

2. Signaling and function of BDNF in healthy brain tissue

As mentioned previously, neurotrophin BDNF is a key molecule in modulating neuroplasticity in the brain. It supports neuronal growth, survival, differentiation, and repair (Lin & Huang, 2020). BDNF is produced in various regions of the brain, but is also produced in the lungs, heart, spleen, gastrointestinal tract, and liver (Bathina & Das, 2015). BDNF can cross the blood-brain barrier after excretion. In previous studies serum and plasma BDNF levels have shown a correlation with BDNF levels in cerebrospinal fluid. Due to this correlation, serum BDNF levels are used as a biomarker for protein levels in the brain (Chiou & Huang, 2017).

2.1 Functions of BDNF

To understand how BDNF may play a role in the development of schizophrenia, it is important to understand its functions in healthy tissue. These include neuronal development, neurogenesis, and synaptic transmission, and will now be described in more detail. BDNF has shown to be important in the regulation of several neuronal processes. Two of these processes are neuronal development and survival. The role of BDNF in this process is one of the earliest identified functions of BDNF (Bathina & Das, 2015). Neurogenesis, the formation of new neurons in the brain, mainly occurs in neural progenitor cells in the lateral ventricles and the hippocampal dentate gyrus, where other neuronal processes are also facilitated. These processes will be discussed later in this section (Numakawa et al., 2017). All neurotrophin peptides are vital to regulation of neurogenesis, although BDNF has shown to be required for a basal level of this process. Further studies have shown that neurogenesis is reduced in Tropomyosin receptor kinase B (TrkB) knockdown mice. These results suggest that the effect of BDNF occurs through the TrkB pathway (Liu & Nusslock, 2018).

Expression levels of BDNF fluctuate in individuals in adulthood. Regulation of the expression of BDNF and serum BDNF levels is influenced by neuronal activity (Palomer et al., 2016), exercise (Elmquist et al., 2016), and hormones such as estradiol (Wei & Berman, 2019) among others. Studies have shown that exercise results in enhancement of hippocampus-related memory function and increased serum BDNF levels (Griffin et al., 2011). Interestingly, BDNF levels have shown to be decreased in both the aging population and individuals with pathological conditions such as psychiatric or neurodegenerative disorders. The protein deficits seen in pathological conditions make BDNF an important biomarker for psychiatric diseases such as Schizophrenia (Miranda et al., 2019). The exact mechanism of exercise in the increase of serum BDNF will be described later in section 4.2. In conclusion, the mentioned studies indicate that BDNF is important in many neuronal processes in healthy tissue. In the following section gene composition and regulation will be described of the *BDNF* gene.

2.2 *BNDF* gene composition and regulation

To understand the dysregulation of the *BDNF* gene in schizophrenia, it is important to understand the gene composition and regulation. These will be explained in more detail in the following section. The human *BDNF* gene is located on chromosome 11 and consists of 11 exons in total. Expression of the gene is regulated by 9 individual promoters and epigenetic modifications. These promoters lead to the synthesis of different transcripts of the *BDNF* gene by generating alternative combinations of promoters and splice products. The sequence comprises 9 exons, in which exon 9 contains the coding sequence of pro-BDNF. The 8 upstream exons encode promoters that regulate regional expression. This is called selective expression, which can control expression in different subcellular compartments. The alternative splicing variants create distinct polyadenylation sites and alternative splice sites, although all of them encode for one pro-BDNF protein product. Exon 4 has been characterized as regulating activity-dependent *BDNF* expression (Cattaneo et al., 2016; Maynard et al., 2016). The structure of the human *BDNF* gene is shown in figure 3.

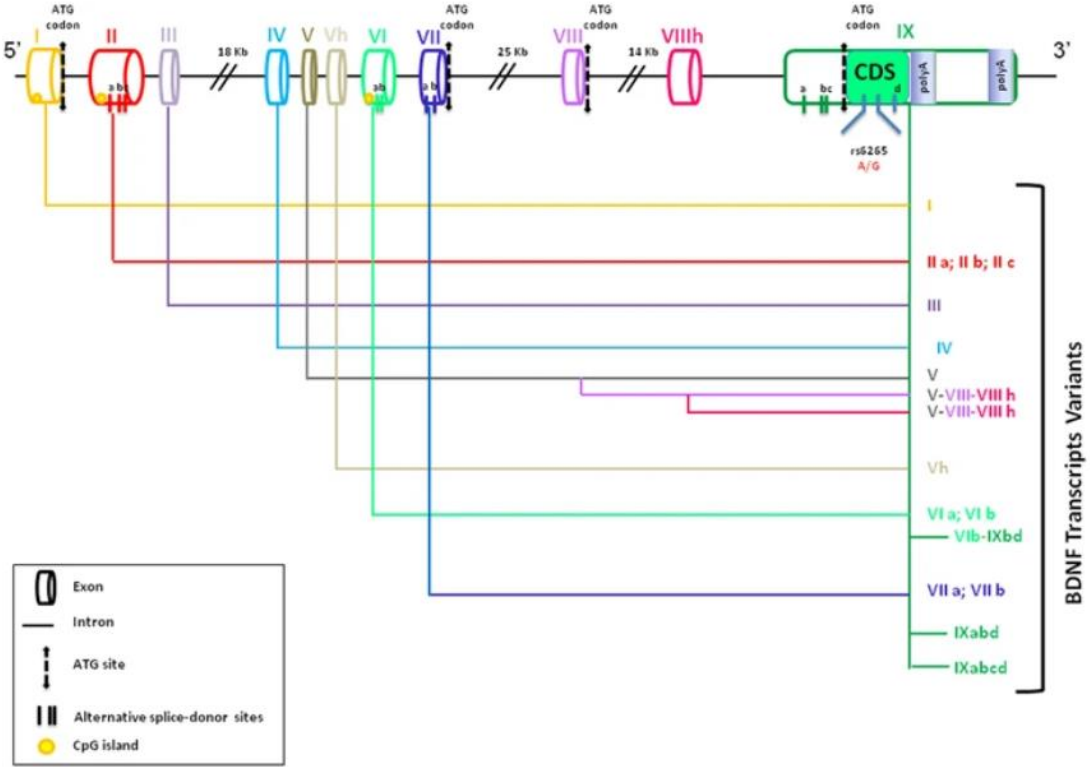

Figure 3: Human BDNF gene structure. the gene comprises 11 exons that combine to form different transcripts. Introns, ATG sites, alternative splice-donor sites and CpG islands are also shown. The coding DNA sequence (CDS) is the region that encodes the sequence for pro-BDNF.
(Cattaneo et al., 2016)

Epigenetic modifications important in *BDNF* expression regulation both repress and activate transcription of the *BDNF* gene. One such modification is the methyl-CpG binding protein 2 (MeCP2), which represses gene transcription. MeCP2 binds to methylated DNA at promoter IV and forms a complex with Sin3a and histone deacetylase 1 (HDAC1). This complex maintains the repressed state of the gene (Boulle et al., 2012). Other epigenetic mechanisms that regulate gene expression are histone

modifications and non-coding RNAs (Zheleznyakova et al., 2016). Finally, expression of *BDNF* is regulated by activation of the cyclic AMP response element (CRE) and its binding protein (CREB). CRE is activated through the cAMP/protein kinase A (PKA) pathway (Lee et al., 2010). Signaling through this pathway is also induced by binding of BDNF to its receptor. This pathway will later be explained further in section 2.3.

Synthesis and cleavage of the precursor protein occurs in the endoplasmatic reticulum. This protein is also called a signal peptide, which is converted to pro-BDNF. Pro-BDNF is either stored for secretion or converted to mature BDNF by endoproteases, such as furin, in the Golgi complex. If secreted as pro-BDNF, the protein is cleaved at the extracellular level by matrix metalloproteinases or plasmin to generate mature BDNF (Cattaneo et al., 2016). As previously mentioned, precursor molecule pro-BDNF is also secreted by axons in an activity-dependent manner. Although both pro-BDNF and mature BDNF are neurologically active, both peptide molecules follow a different mechanism of action and elicit opposing effects (Je et al., 2012). In conclusion, the *BDNF* gene has a comprehensive composition, in which regulation is important to ensure the correct expression in healthy tissue. In the following section cellular signaling in target cells in further described.

2.3 Intracellular signaling in target cells

To understand how dysregulated signaling in target cells through BDNF may play a role in schizophrenia, it is necessary to understand BDNF signaling in healthy neuronal cells. This signaling includes multiple pathways to ensure that functions of BDNF can be carried out, and these will now be explained in more detail. Pro-BDNF is released by axons following an action potential and bind to the p75 neurotrophin receptor ($p75^{NTR}$) on the soma of other neurons where they induce intracellular signaling. Internalization of the receptor follows binding of pro-BDNF, which moves into early endosomes. The receptor associates with a variety of co-receptors, although association with a sortilin protein allows binding of pro-BDNF (B. Yang et al., 2017). $P75^{ntr}$ activates various transmembrane proteins, including tropomyosins, Nogo and myelin associated glycoprotein (MAG). These pathways result in apoptosis or programmed cell death, signal transduction, gene expression regulation and organization of extracellular matrix (Sajanti et al., 2020).

BDNF itself is released after an increase of intracellular calcium following an action potential. After secretion it acts as a local factor at the synaptic cleft and binds with high affinity to the TrkB receptor, located on the membrane of an adjacent cell. After binding slow and fast signaling cascades are induced inside the cell. The receptor dimerizes upon binding, which activates the kinase activity of the intracellular tail. The kinase phosphorylates tyrosine and serine residues to link SCR homology 2 domain containing protein (Shc) and phospholipase C-gamma (PLCy), which causes different intracellular signaling cascades. Phosphorylation of Shc induces activation of rat sarcoma (Ras) GTPase, extracellular signal-regulated kinases (ERK) and protein kinase B (Akt) after numerous signals. Both signaling cascades lead to activation of transcription factors mTOR, MNK1 and RSK to mediate gene expression. Phosphorylation of a second tyrosine residue creates a binding site for PLCy. This linkage induces release of calcium ions from the endoplasmatic reticulum through inositol triphosphate (IP_3) and diacylglycerol (DAG) increase and activates calmodulin-dependent protein kinase 2 (CaMKII). During this release phosphorylation of serine residue 478 on TrkB induces a linkage of nucleotide exchange factor TIAM1. TIAM1 activates Rac1 through exchanging a guanine nucleotide. Both pathways are shown in figure 4 (Sasi et al., 2017).

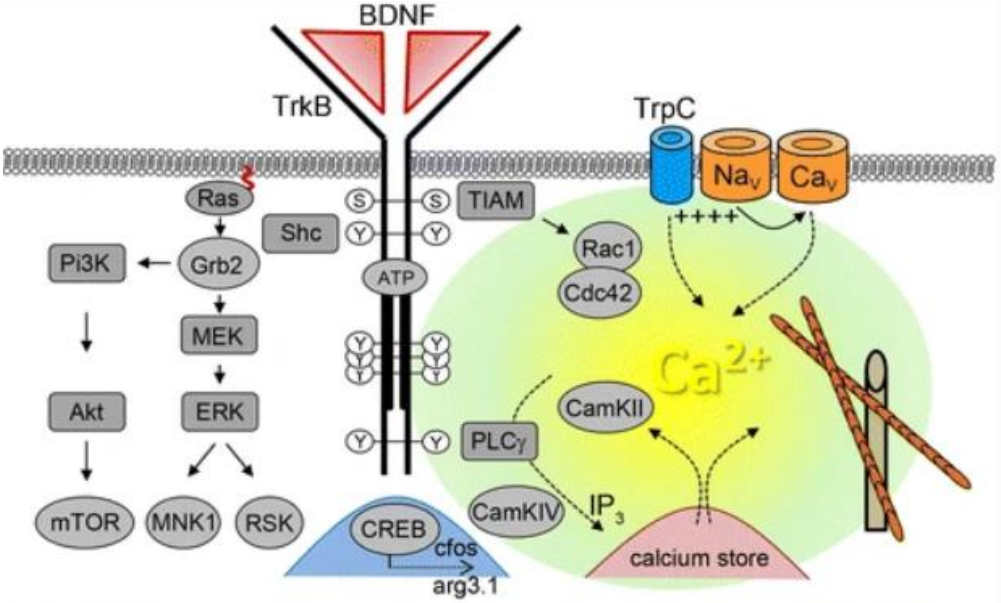

Figure 4: BDNF/TrkB signaling in neuronal cells. Binding of BDNF leads so multiple signaling pathways in neuronal target cells for neuronal differentiation and synaptic plasticity. Details are explained in the main text. (Sasi et al., 2017)

Signaling through BDNF/TrkB activates one or both transcription factors cyclic AMP response-element binding protein (CREB) and CREB-binding protein (CBP). These transcription factors regulate gene expression for genes involved in maintaining cell and brain functions (Bathina & Das, 2015).

As mentioned previously, one of these cell functions is neurogenesis. Neurogenesis enhances long-term potentiation (LTP) in the hippocampus, which is amplified by mediation of synaptic plasticity by BDNF. Early studies shown that BDNF is upregulated by stimulation that leads to LTP through activation of PLCy and induction of CREB and CAMK (Minichiello et al., 2002; T. Yang et al., 2020). More recent studies also show BDNF-TrkB signaling at synapses during LTP consolidation (Panja et al., 2014). Postsynaptic functions during this process also include increase of AMPA receptor activation. AMPA receptor activation induces actin polymerization and spine head enlargement. In this manner the postsynaptic function of BDNF also facilitates synaptic plasticity in the dentate gyrus (T. Yang et al., 2020).

In the adult brain, BDNF mediates both excitatory and inhibitory synaptic transmission and is induced in an activity-dependent manner. Studies have shown that ERK signaling in neurons contributes to dopamine and glutamate signaling. This results to the enhancement of excitatory synaptic transmission and persistence of long-term memory (Morella et al., 2020). In inhibitory synaptic transmission activation of TrkB receptors causes mobilization of 2-arachidonolglycerol (2-AG). 2-AG acts on and activates presynaptic cannabinoid 1 (CB1) receptors, which in turn aids BDNF in reducing presynaptic release of GABA. Another mechanism of BDNF to suppress GABAergic signaling involves mobilization of endogenous CBs (eCBs). It is likely that generation of 2-AG leads to release of eCBs to suppress GABAergic neurotransmission. This has mainly been seen in the hippocampus and somatosensory cortex. The effect of BDNF is enhanced in regions with higher levels of expression (Selvam et al., 2019). In short, BDNF induces multiple intracellular signaling cascades to carry out

functions of neural plasticity and neurogenesis among others. In the following section altered signaling in schizophrenia will be explained.

3. Altered BDNF gene expression and signaling in Schizophrenia

3.1 Val66Met polymorphism and epigenetic mechanisms

To determine the role of BDNF in development of schizophrenia, understanding the effect of dysregulation of the gene is essential. These include the Val66Met polymorphism and epigenetic mechanisms that will be explained in more detail. A naturally occurring single-nucleotide polymorphism (SNP) in the *BDNF* gene is the substitution of a guanine to an adenine at position 196, which is also called G196A or rs6265. The substitution results in an amino acid residue shift from valine to methionine at position 66, also called Val66Met. This SNP is observed in over 25% of the human population and influences the release of the BDNF protein in an activity-dependent manner (Park et al., 2017) (Anastasia et al., 2013). Val66 is located in the BDNF prodomain which mediates interaction with sortilin. Sortilin acts as a chaperone and aids in transporting pro-BDNF to the secretory pathway. A substitution of Met66 does not change protein structure but shows decreased binding to sortilin and eventually a reduction in secretion of BDNF. The decrease in BDNF leads to altered synaptic plasticity (Anastasia et al., 2013). In individuals carrying a Val66- and Met66-coding allele both alleles are expressed simultaneously. However, studies suggest that the Val66-coding allele variant is partially dominant to the Met66-coding allele variant. This dominance results in a decrease in *BDNF* expression in heterozygous or homozygous individuals carrying the Met66-variant (de Assis et al., 2021).

Changes in expression of *BDNF* have been associated with psychiatric disease. The decrease in BDNF secretion leads to altered signaling in target cells, influencing dendritic growth and synaptic communication (Schweiger et al., 2019). Important factors that cause a change in *BDNF* expression are epigenetic mechanisms. Postmortem brain tissue of psychiatric patients showed a higher DNA methylation level in the promoters of the *BDNF* gene compared to healthy individuals. Recent studies also showed an increase in histone modification, specifically H3K9Me2. The histone is located at *BDNF* exon IV and it represses gene promoters. Histone methylation could also possibly lower BDNF levels in patients (Hsieh et al., 2019). A final epigenetic mechanism that has been shown to possibly play a role in *BDNF* gene expression is the microRNA miR-183. This microRNA can inhibit translation of mRNA through post-transcriptional gene silencing. However, studies have shown varying results when studying this mechanism (Lin & Huang, 2020). In conclusion, studies indicate that genetic modifications lead to altered gene expression in schizophrenia patients. In the following section the effect of altered gene expression on signaling in target cells is described.

3.2 Altered signaling in target cells

To understand the consequences of this *BDNF* gene dysregulation in target cells it is important to understand altered signaling. This includes reduced TrkB signaling, 5-HT dysfunction, and dysfunction in dopamine signaling, which will be described in this section. A reduction in BDNF secretion causes a reduction in TrkB signaling in target cells. This leads to a decrease in TrkB-TK mRNA in temporal regions and in the prefrontal cortex. In healthy individuals, BDNF regulates maturation of GABA neurons through TrkB signaling, suggesting that decreased signaling possibly leads to abnormalities in these neurons (Ray et al., 2011). This conclusion is supported by other studies, which show a decrease in GABA-A receptor availability in patients. GABA-A receptors are mainly concentrated in limbic regions such as the hippocampus. In healthy individuals, GABAergic neurotransmission plays an important role

in the inhibition of neuronal activity of pyramidal neurons. The reduction of GABAergic signaling leads to hippocampus hyperexcitability, which leads to symptoms typically seen in schizophrenia (Marques et al., 2021).

It is also shown that a loss of BDNF from any promoter causes enhanced aggression. Due to the role of BDNF in promoting 5-HT neuron development and function. Impaired BDNF secretion correlates with 5-HT dysfunction and eventually leads to aggression (Maynard et al., 2016). This impairment corresponds with results found by other studies, which show that *BDNF* knockout mice show increased levels of anxiety and aggression. In healthy individuals, BDNF induces crosstalk with 5-HT to modulate signaling of 5-HT on target cells and vice versa (Bazovkina et al., 2021).

A third pathway that is altered due to decreased BDNF secretion is the dopaminergic system. BDNF promotes differentiation of dopaminergic neurons by performing crosstalk with dopamine (Bazovkina et al., 2021). Crosstalk between BDNF and dopamine leads to amplification of ERK activation in neurons. A decrease in BDNF secretion leads to decreased crosstalk with dopamine receptors (Morella et al., 2020). Studies have shown that patients with schizophrenia show a dysfunction in dopamine signaling in distinct regions of the brain, which can lead to the development of positive and negative symptoms. For example, symptoms such as hallucinations and delusions may be a result from dysfunctional dopaminergic signaling (Mccutcheon et al., 2020). In summary, research indicates that signaling in neuronal cells is strongly dysregulated in multiple ways when looking at schizophrenia patients. However, *BDNF* expression is also influenced by environmental factors, which will be described in the following section.

3.3 Environmental influences on *BDNF* expression

To determine causes of schizophrenic development prior to *BDNF* dysregulation, it is important to understand the effect of environmental influences on *BDNF* expression. These include the number of depressive episodes, childhood trauma experiences, aging, disease, and stress. The number of depressive episodes and childhood trauma experiences will now be explained in further detail. As mentioned previously, schizophrenia is a multifactorial disorder (Picchioni & Murray, 2007). Influences outside of genetical makeup have been shown to have an effect on the secretion of BDNF. One such influence is the number of depressive episodes during the course of the illness. Studies show that patients with more depressive episodes showed reduced plasma BDNF levels. It is also shown that patients remaining in a longer depressive episode showed lower BDNF levels (Aas et al., 2019). Other research shows lower BDNF serum levels in patients during their first depressive episode. These results suggest that decrease in BDNF serum levels occurs during the onset of the illness. The reduction in BDNF possibly leads to an individual being more susceptible to develop schizophrenia (di Carlo et al., 2020).

A second influence on plasma BDNF levels has shown to be childhood trauma experiences. Experiences of childhood trauma have shown to be negatively correlated with BDNF levels compared to healthy individuals. This is possibly due to a dysregulated brain development during childhood. Stress induced during the experience reduces *BDNF* mRNA levels in the hippocampus, leading to more severe symptoms. This development may also lead to a more progressive illness accompanied by more episodes (Aas et al., 2019). Childhood trauma also leads to a state of chronic stress. Chronic stress in an individual leads to reduction of BDNF hippocampal expression and thus to cognitive and synaptic deficits (Miranda et al., 2019).

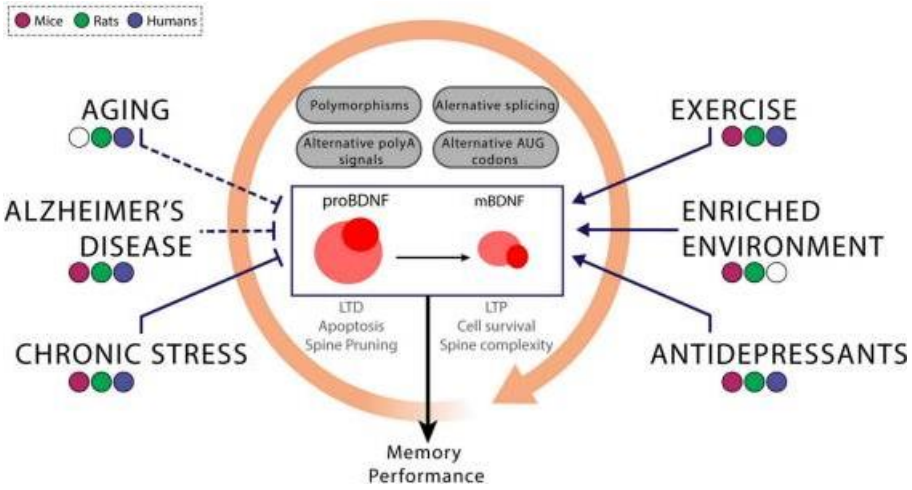

Figure 5: Interplay between different factors in expression of BDNF. Different factors are shown that influence expression of the BDNF gene. Different organisms appear to show these effects and are indicated by the colored dots: Mice (purple), Rats (green) or Humans (blue). (Miranda et al., 2019)

In conclusion, many factors influence the expression of the BDNF gene in a healthy and diseased individual, which is shown in figure 5. Aging, Alzheimer's disease and chronic stress are related to reductions in BDNF levels in diseased individuals, in combination with genetic mechanisms such as polymorphisms and alternative splicing. Exercise, antidepressants, and an enriched environment however are able to enhance *BDNF* expression. Therefore, these factors have been given attention as possible treatment options (Miranda et al., 2019). The options of exercise and antidepressants will be further discussed in section 4.2.

4. The effect of antipsychotics on BDNF levels in schizophrenia

4.1 The effect of antipsychotic agents

To understand how BDNF may play a role in the treatment of schizophrenia, it is essential to understand the effect of antipsychotic drugs on BDNF levels. In this section, effect of three antipsychotic agents on BDNF levels is reviewed in more detail, which are clozapine, olanzapine, and chlorpromazine. As an individual is diagnosed with schizophrenia, different treatment options are selected. Treatment options may either be nonpharmacological (therapy) or pharmacological (antipsychotics, antidepressants) (Patel et al., 2014). Antipsychotic treatment can be divided into two categories. Typical, or first-generation antipsychotics are an older type that is still prescribed today. Atypical, or second-generation antipsychotics are a newer type developed since 1970 until now (Abou-Setta et al., 2012).

One such atypical antipsychotic treatment is clozapine. Clozapine is widely used in treatment of schizophrenia patients (Li et al., 2019). Clozapine was first synthesized in 1956 and has since shown to be more effective than other antipsychotics. The drug also shows to have other advantages in comparison to other drugs, such as an improvement of cognition and a lower risk of suicide (Haidary & Padhy, 2021). Clozapine is a dopamine receptor antagonist and selective serotonin receptor agonist

that binds to $D_{1\text{-}5}$ and 5-HT_{2A} receptors. The agonist feature activates Akt signaling through the serotonin receptor which reduces negative and cognitive symptoms (Stępnicki et al., 2018). The antagonistic properties of clozapine on both receptors may lead to increased expression of *BDNF* through cellular signaling. Other manners to increase *BDNF* expression are the ability of clozapine to increase acetylcholine and dopamine secretion in the hippocampus and prefrontal cortex. Finally, the effect on hippocampal CREB may influence the expression of *BDNF* (Ertuğrul et al., 2011). The hypothesis that clozapine has an effect on serum BDNF levels has been debated for quite some time, since it was shown that serum BDNF levels positively correlated with clozapine doses in schizophrenic patients (Grillo et al., 2007). Other recent studies have shown an increase in *BDNF* mRNA expression after prolonged administration with clozapine in the prefrontal cortex of animal models (Li et al., 2019). However, other studies have also reported no significant change in *BDNF* expression after administration of clozapine compared to controls (Ertuğrul et al., 2011).

A second atypical antipsychotic drug with proven efficacy for treatment of schizophrenia is olanzapine. Olanzapine was first approved in 1996 and has shown a reduced risk of motoric adverse effects. However, olanzapine has been positioned as a second-choice therapy due to an increased risk of metabolic dysregulation (Citrome et al., 2019). Olanzapine is a dopamine D_2 receptor and 5-HT_{2A} receptor antagonist that loosely binds and allows normal dopamine neurotransmission. This antagonistic feature causes a decrease of positive and negative symptoms in patients (Thomas & Saadabadi, 2021). Studies have shown an increase in activity of the *BDNF* gene promotor and an increase in BDNF levels after treatment with olanzapine through CREB-mediated gene transcription. Another possibility is the involvement of protein kinase C (PKC) and CMKII in mediating *BDNF*, although evidence for interaction between olanzapine and these signaling factors has not been found (Lee et al., 2010). However, other studies shown a decrease in *BDNF* and CREB expression after olanzapine administration. This possibly suggests that treatment of patients with olanzapine is less effective in treating negative symptoms compared to other antipsychotic drugs in general (Gumuslu & Mutlu, 2019).

A third antipsychotic drug that is used for treatment of schizophrenia is chlorpromazine. Chlorpromazine is the first effective antipsychotic drug discovered and is still listed as one of five medicines used in psychotic disorders. Chlorpromazine is a typical antipsychotic drug that was first synthesized in the 1950s. This drug is also a dopamine D_2 receptor antagonist which binds more permanently compared to atypical antipsychotics. Lack of selectivity also causes blocking of alternative dopamine pathways. This effect would suggest that administration of chlorpromazine leads to similar effects as clozapine (Dudley et al., 2017). Previous studies have shown however, that chlorpromazine does not relate to an increase in BDNF levels (Fernandes et al., 2015). The actual effect of chlorpromazine on BDNF levels has shown conflicting data in performed studies. This is due to aberrant factors when carrying out experiments, such as differing doses (Chiou & Huang, 2017). All three drugs mentioned above bind mainly at the dopamine receptor, though different receptors are also targeted. Target receptors of all three agents are shown in figure 6.

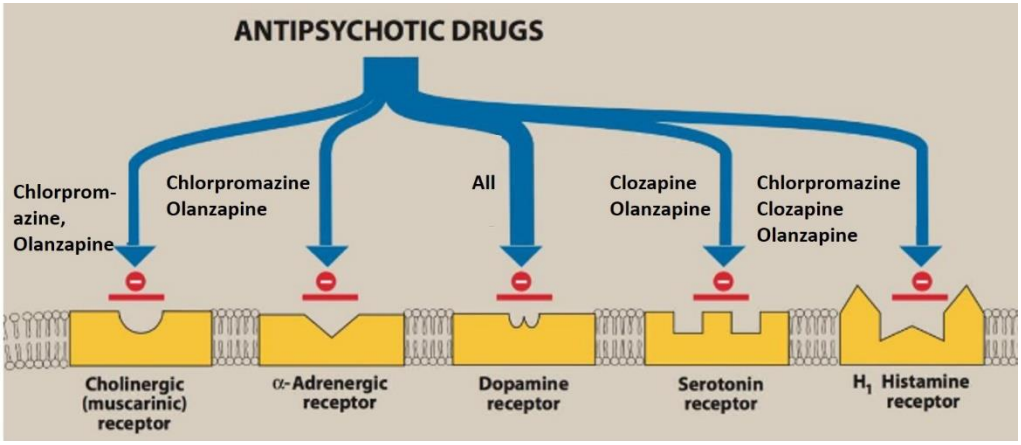

Figure 6: Targeted receptors of antipsychotic agents chlorpromazine, olanzapine and clozapine. Receptors affected by these agents are the cholinergic, α-adrenergic, dopamine, serotonin and histamine receptor.

In general, multiple antipsychotic treatments have shown to lower BDNF levels or *BDNF* mRNA in the brain of animal models. In humans, antipsychotics have also shown to induce alterations in BDNF levels (Chiou & Huang, 2017). Clozapine, olanzapine, and chlorpromazine have each shown to increase BDNF levels in schizophrenic patients, although some studies have shown conflicting results when measuring BDNF levels. The effect of these antipsychotic agents might be enhanced by other possible treatment options, which will be further specified in the following section.

4.2 The effect of other possible treatment options

To understand how schizophrenia can be treated when using antipsychotic agents in combination with other possible treatment options, the effect of these other options on BDNF levels needs to be assessed. In addition to pharmacologic antipsychotic treatment for schizophrenia, treatment options are personalized for patients. These options may be exercise and therapy among others. Exercise has been shown to increase BDNF levels, hippocampal volume, neurogenesis and synaptic plasticity. During these structural changes, BDNF mediates the effect of exercise on synaptic plasticity by remodeling affected axons and dendrites (Girdler et al., 2019). Multiple theories have been researched and found that explain the manner in which exercise can lead to increase of BDNF levels. Studies have shown that physical exercise increases the accumulation of an endogenous molecule D-β-hydroxybutyrate (DBHB) in the hippocampus. This molecule crosses the blood-brain barrier and acts as a regulator of *BDNF* transcription through inhibition of class 1 HDACs. Inhibiting HDACs specifically induces *BDNF* expression by altering the binding of HDACs to the *BDNF* promoter (Elmquist et al., 2016). The effects of exercise on *BDNF* expression are only visible in specific regions in the brain, mostly the hippocampus, cerebellum, and frontal cortex. These changes, in turn, correlate with the effects on memory performance, improved cognitive outcome and overall prevention of neurodegenerative and psychiatric disorders (Miranda et al., 2019).

Exercise as a treatment is often carried out in combination with antidepressants. Since depression is a common symptom in schizophrenic patients, antidepressants are often prescribed. Antidepressants have shown to improve depressive symptoms in schizophrenic patients when used in combination with antipsychotics (Mao & Zhang, 2015). In addition to suppressing depressive symptoms, antidepressants have also shown to increase expression of *BDNF* in the hippocampus. These effects are seen when

antidepressants are administered in combination with acute ketamine treatment, but also without additional treatments. This eventually leads to neurogenesis, axon elongation, dendritic sprouting, and expression of plasticity-related proteins (T. Yang et al., 2020). It has recently been discovered that antidepressants bind to the transmembrane domain of TrkB dimers. This binding leads to a conformational change and translocation to a more favorable location at the plasma membrane. At this location the receptor is more accessible to BDNF, and binding of BDNF leads to the intracellular signaling explained previously (Casarotto et al., 2021). In conclusion, the mentioned studies indicate that exercise and antidepressants mediate the increase of BDNF levels in schizophrenic patients. The increase of BDNF leads to enhanced neuronal functioning and modeling, which lead to improved cognitive outcome.

5. Discussion

It has been shown that BDNF plays a significant role in neurodevelopment, neurogenesis, synaptic remodeling and memory (di Carlo et al., 2020). Due to the important function, the dysregulation of BDNF plays a significant role in the development of schizophrenia, which is corroborated by multiple studies (Boulle et al., 2012; di Carlo et al., 2020). However, many aspects of this molecule in the brains of schizophrenia patients can still be assessed in the future. Some of these possible future aspects will be further explained in the following sections. Studies to examine BDNF in healthy and diseased individuals also have limitations that have not been assessed previously in this review. Some of these limitations will also be described in relation to their effect on BDNF in individuals.

One possible aspect to assess in the future is the brain structure of schizophrenic patients. It is known that these patients show different subtypes of brain structures which may have different effects on development and onset of the illness (Chand et al., 2020). The effect of the *BNDF* Val66Met polymorphism, mentioned previously, on brain structure has shown conflicting results (Miranda et al., 2019). In future studies, the exact differences in brain structures between healthy and schizophrenic individuals should be further assessed to study the pathophysiology of this psychotic disorder. This could be done by different brain imaging techniques to assess brain function and to determine the exact cause of altered brain functions.

Overall, the dysregulation of BDNF may have different effects in different brain areas and in general in neuronal networks (T. Yang et al., 2020). These effects have been studied intensively, although the exact mechanism of action in each brain region is still largely unknown. Diagnosing schizophrenia using the DSM-IV is based on symptoms that are a result of dysregulation of neuronal networks. In conclusion, these neuronal networks are the key to understanding the origin of schizophrenic symptoms. A next step in future studies should be to try to fully understand these neuronal networks and the role of BDNF in altering the strength and functioning of these networks. After this assessment, there is a potential to develop a new type of second-generation antipsychotic agents to specifically target highly involved pathways in certain brain regions.

As mentioned previously, in this literature review many factors have not been taken into account when looking at the function of BDNF has in healthy individuals and individuals with schizophrenia. One such factor are bodily differences between schizophrenic patients. Sex differences have shown to cause

significant differences in BDNF levels. Female schizophrenic patients have increased plasma BDNF levels compared to mail schizophrenic patients (Weickert et al., 2019). This difference can be a result of the potential of sex hormones, mainly estradiol, to regulate BDNF levels (Wei & Berman, 2019). These sex differences potentially influence the age of onset of schizophrenia, as well as an accelerated development of the illness in males. These possibilities could be further explored in future studies to determine whether an increase in BDNF in females is beneficial to cognitive abilities. A final remark to take into consideration is the fact that gender might also significantly influence the efficacy of antipsychotic treatment (Chen & Huang, 2011). This is also an effect that should be studied further. Other bodily differences are the amount of stress and physical exercise across the lifespan of an individual (Miranda et al., 2019). These differences also both lead to different effects that the *BDNF* gene can exert in the body (Miranda et al., 2019). This also needs to be taken into account when looking at the effects of BDNF.

The use of BDNF as a biomarker in schizophrenia has been utilized by multiple studies assessed in this review. This is done because serum BDNF levels show a correlation with BDNF levels in cerebrospinal fluid, as mentioned previously (Chiou & Huang, 2017; Y. Zhang et al., 2018). However, other studies have shown that BDNF is dysregulated in many pathological conditions. The effect of BDNF dysregulation in neurodegenerative and neuropsychiatric diseases indicate the importance of BDNF not only in schizophrenia (Miranda et al., 2019). Other studies suggest peripheral BDNF levels cannot be considered a biomarker for psychiatric symptoms at all (Cattaneo et al., 2016). These results show that BDNF may not be a valid biomarker in schizophrenia explicitly but in neuropsychiatric disorders overall. As further studies are carried out to investigate BNDF levels in relationship to schizophrenia, it is important to take these findings into account. Enhanced BNDF levels may not only be an indication of schizophrenia but also other psychiatric disorders.

Although the use of BDNF as a biomarker in schizophrenia is debatable, it is still an important factor in the development of schizophrenia. Treatment of the illness has shown to have an effect on levels of BNDF, mostly increasing these levels when administered (Ertuğrul et al., 2011; Lee et al., 2010). In this review only the effect of three antipsychotic drugs on BNDF levels has been investigated, while many more antipsychotic agents might have a similar or different effect. The mechanism of action and result when using these agents can be explored further. The effect of various antipsychotic agents on BDNF levels is largely unknown and future research might be able to uncover these (Chiou & Huang, 2017). According to recent studies, BDNF signaling could be considered a possible target in pharmacogenetic therapy. However, a gene-based association study suggested that the *BDNF* gene is involved in treatment resistance. Minor allele homozygotes were more likely to be resistant compared to major allele homozygotes and heterozygotes (J. P. Zhang et al., 2013). The BDNF signaling pathway could be a major target for pharmacogenetic drugs. This still needs to be explored further to determine the mechanism of drug resistance before new drugs could be designed and synthesized.

Overall, the development of schizophrenia occurs through a combination of many causes. These causes cannot lead to schizophrenia independently of each other, meaning that development of this illness is a process of various stages in certain brain areas. However, as has been stated in this review, one neurotrophin that plays a significant role is BDNF. In healthy individuals, this protein plays a significant role in neurogenesis and synaptic plasticity. In the schizophrenic brain, a combination of genetic polymorphisms, epigenetic regulation, altered signaling and environmental influences lead to

dysregulation of the *BDNF* gene or its translated protein. The altered signaling leads to neurodegeneration, positive and negative symptoms. Antipsychotic or alternative treatment can lead to the enhancement of the *BDNF* gene and increase of BDNF levels. The importance of the gene in schizophrenia makes it an important possible target in treatment of schizophrenic patients and possibly other psychological conditions. The future of schizophrenic research might be in determining the pathophysiology of this psychotic disorder. An important next step would be to examine the exact cause of altered brain functions. Following this research, it might be possible to try to fully understand the role of BDNF in altering these neuronal networks and to develop a new type of antipsychotic agent to target these pathways in specific brain regions.

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