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The Physiology of BDNF and Its Relationship with ADHD

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Abstract Brain-derived neurotrophic factor (BDNF) is a major neurotrophin in the central nervous system that plays a critical role in the physiological brain functions via its two independent receptors: tropomyosin-related kinase B (TrkB) and p75, especially in the neurodevelopment. Disrupting of BDNF and its downstream signals has been found in many neuropsychological diseases, including attention-deficit hyperactivity disorder (ADHD), a common mental disorder which is prevalent in childhood. Understanding the physiological functions of BDNF during neural development and its potential relationship with ADHD will help us to elucidate the possible mechanisms of ADHD and to develop therapeutic approaches for this disease. In this review, we summarized the important literatures for the physiological functions of BDNF in the neurodevelopment. We also performed an association study on the functional genetic variation of BDNF and ADHD by a case-control study in the Chinese mainland population and revealed the potential correlation between BDNF and ADHD which needs further research to confirm.

Keywords BDNF · Neural development · ADHD · Val66Met

Introduction

Among the well-known neurotrophins, brain-derived neurotrophic factor (BDNF) is the most abundant and widely distributed one in the mammalian central nervous system (CNS) [1]. In 1982, BDNF was shown to promote survival of a subpopulation of dorsal root ganglion neurons and subsequently purified from pig brain [2]; since then, a great deal of evidences have mounted for its vital roles in brain development, physiology, and neuropsychiatric diseases, including ADHD, a common psychiatric disorder in childhood that is characterized by pervasive and developmentally inappropriate inattention, excessive motor activity, impulsivity, and distractibility [3]. Due to its high prevalence worldwide (approximately 3–9 %) [4] and severely vicious impact on the quality of life, it is necessary to understand the pathogenesis of ADHD. During the past few years, the etiology of ADHD has been widely studied, and many neurochemical factors are suggested to be crucial in the pathogenesis of ADHD [5]. Meanwhile, BDNF plays a key role in the survival and differentiation of midbrain dopaminergic neurons [6]. A decreased midbrain BDNF activity may cause midbrain dopaminergic dysfunction, and therefore, resulting in ADHD [7].

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Structure of BDNF

The human BDNF gene is located at chromosome 11p14.1 [8]. There are four exons (exons I–IV) associated with distinct promoters located in 5′ terminal, while one 3′ exon (exon V) encodes the mature BDNF protein [9]. BDNF has eight different transcripts, and the transcripts consisting of exons I–III are predominantly expressed in the central nervous system and with exon IV are distributed in the heart and lung [10] (Fig. 1). BDNF in different mammals is highly conserved not only in the amino acid sequence but also in the tissue distribution. The two BDNF monomers are always binding together via non-covalent bonding to form a dimer and then bind with their receptors, which in turn initiate the intracellular signal transduction [11]. There are two forms of BDNF proteins: immature precursor BDNF protein (pro-BDNF) and mature BDNF protein (mBDNF); each of them possesses different binding characteristics and distinct biological activity [12].

Metabolism of BDNF: Distribution, Synthesis, Release, and Expression

Distribution

BDNF is distributed throughout the whole central nervous system and highly concentrated in the hippocampus and cerebral cortex [13], including the frontal-striatal-cerebellar circuits and ventral striatal-limbic circuits, two important circuits that are critical for the pathogenesis of ADHD [14]. During the development, BDNF is low while the level of BDNF goes up to a much higher level postnatally [15]. Indeed, it is the most abundant and broadly distributed neurotrophic factor in the adult brain [16].

Synthesis

In the mammalian brain, the precursor of BDNF, pro-BDNF is first synthesized in the endoplasmic reticulum and then is proteolytically cleaved to generate mature BDNF (Fig. 2). Pro-BDNF is a 32-kDa protein with 247 amino acids consisting of an N-terminal pro-domain and a C-terminal mature domain (mBDNF) with a N-linked glycosylation site [17, 18]. After the initial generation, most of the pro-BDNF molecules are packaged into vesicles and then undergo N-terminal cleavage by multiple extracellular proteases, such as plasmin [19], tPA/plasmin cascade [20], metalloproteinase gene matrilysin (MMP7) [20], and extracellular matrix metalloproteinases [21]. In trans-Golgi complex, the pro-BDNF was cleaved in the pro-region, leading to the production of mature BDNF (14 kDa); a biologically active form is then released mainly by the neurons through constitutive secretion or in an activity-dependent manner. There is another subtype of pro-BDNF, a 28 kDa protein which is not necessary for the generation of the mature BDNF that was identified by immunoprecipitation with BDNF antibodies [18]. Compared to healthy controls, serum BDNF levels were significantly lower in adults with ADHD, suggesting that low BDNF levels may contribute to the neurodevelopmental deficits of ADHD and to the persistence of the disorder into adulthood [22].

Release

The messenger RNA (mRNA) and protein of BDNF are almost distributed in the whole cortical regions, including neuronal soma and dendrites. Most of BDNF is stored or secreted from nonneuronal cells, such as the ependymal cells, astrocyte, and arterial epithelium [23]. The mature BDNF should be released to exert its physiological functions after folding correctly. There are two types of releasing models for BDNF, spontaneous release and stimuli-response release. It is suggested that the pro-domain of BDNF plays an important role in the regulation of its intracellular trafficking to secretory pathway [24]. A single nucleotide polymorphism in the BDNF gene leading to a Val to Met substitution at position 66 in the pro-domain (Val66Met), an important mutation involved in ADHD, alters the trafficking of wild-type BDNF via the formation of heterodimers which are less efficient in sorting and secreting [25]. Compared with healthy controls, the serum level of BDNF is significantly lower in adult ADHD patients [22], while higher in children [26, 27].

The Regulation of BDNF Expression

The expression of BDNF can be regulated by multiple factors (Fig. 2).

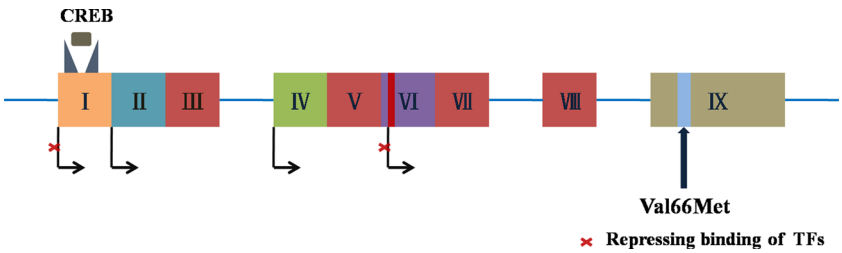

Fig. 1 The genetic structure of human BDNF gene. The binding sites for CREB and the Val66Met variant are indicated. The *red cross* means the binding sites for repressing transcriptional factors (TFs)

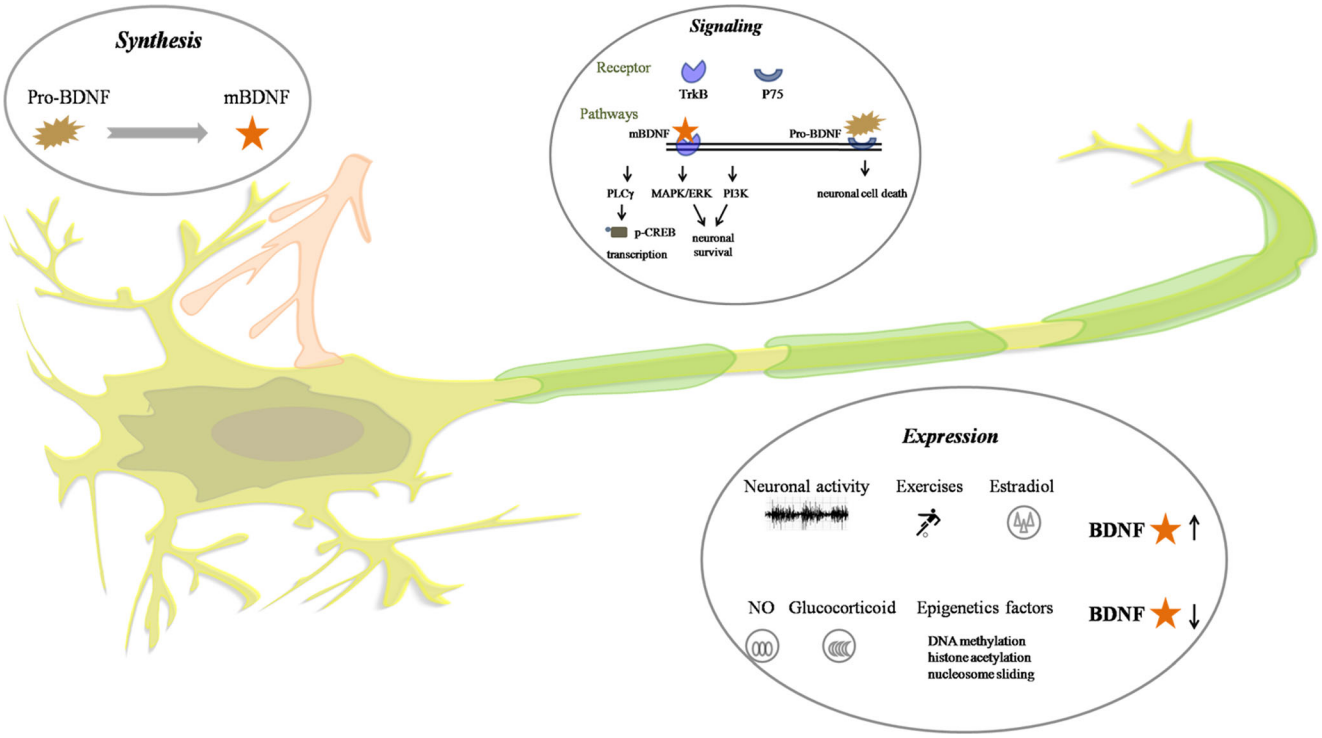

Fig. 2 The synthesis, expression regulation, and signaling of BDNF

Neuronal Activity

In the hypothalamus and cerebral cortex, the synthesis of BDNF is regulated by neuronal activity. For example, glutamate stimulates the expression of BDNF while gamma-aminobutyric acid (GABA) suppresses it. It is also reported that hyperpolarization stimulations as the $GABA_A$ receptor agonists reduces the BDNF level. Furthermore, BDNF and its receptor tropomyosin-related kinase B (TrkB) can also be induced by epileptic seizure, cluster synaptic stimulations, and opioid withdrawal [28].

Nitrogen Oxide (NO)

BDNF is widely distributed in the cell bodies of baroreceptor neurons and can be released from cultured ganglion neurons when the baroreceptors are activated. It is reported that NO level in the baroreceptors regulates BDNF. Application of Nx-Nitro-l-arginine methyl ester, a specific inhibitor of endogenous NO synthases, does not have any significant effect on activity-dependent BDNF release, but leads to upregulation of BDNF expression in an activity-dependent manner [29].

Exercises

Voluntary exercises in mice stimulate the mRNA and protein level of BDNF in the hippocampus, which relies on the activation of acetylcholine-mediated mechanisms. It seems that monoamine signaling is also involved in the BDNF secretion because antidepressant drug treatments increase the monoaminergic synaptic activity concomitantly with the BDNF gene expression increment in the hippocampus [30].

Estradiol

Estradiol can induce the expression of BDNF in the brain. The level of BDNF is decreased in ovariectomy mice while restored after estradiol replacement. Interestingly, the BDNF mRNA level is also recovered after estradiol treatment in gonadectomized male rats [31]. It was reported that estrogen induces BDNF gene expression through an ERE element on the BDNF gene [32] or by a neuronal-activity-dependent manner [33]. Disruption of the relationship between estrogen and BDNF may contribute to neurological and psychiatric diseases, such as Alzheimer's disease [34], depression [35], schizophrenia [36], and ADHD [37].

Glucocorticoid

Glucocorticoid and its receptors had been implicated in the regulation of BDNF expression. Either acute or chronic corticosterone decreases the level of BDNF mRNA in the hippocampal DG area [38]. Meanwhile, glucocorticoid may also regulate the BDNF mRNA degradation, translation, processing, trafficking, and secretion [39]. In ADHD, especially the hyperactive-impulsive type ADHD, the level of cortisol is lower than that in normal children [40]. Disturbance of hypothalamus-pituitary-adrenal axis by excessive exposure

to glucocorticoids in the fetal and early postnatal periods had been also implicated in ADHD [40], while the possible role of glucocorticoid disrupting to BDNF synthesis in ADHD needs to be further studied.

Epigenetics Factors

Epigenetics refers to processes, such as DNA methylation, histone acetylation, or nucleosome sliding, which are dynamic events controlling the expression of genes without affecting the DNA sequence. In recent studies, a lot of epigenetic mechanisms have been associated with BDNF gene regulation in psychiatric disorders. For example, the methyl-CpG-binding protein 2 (MeCP2) selectively binds with the methylated DNA in BDNF promoter IV and repressed the BDNF gene by forming a complex with Sin3a and histone deacetylase 1 (HDAC1) [41]. In the hippocampus of a rodent model of depression, the levels of BDNF mRNA IV and V were decreased, which was associated with long-lasting H3K27 hypermethylation at the corresponding promoters [42].

Signaling of BDNF

Receptors

There are two BDNF receptors on the surface of the cells, TrkB and p75 [43].

TrkB

Tropomyosin-related kinase B (TrkB) is a high-affinity receptor for many neurotrophic factors, such as BDNF, neurotrophin-3, and neurotrophin-4 [43]. It belongs to the large family of receptor tyrosine kinases. Until now, three isoforms of TrkB had been found, and the full-length isoform is a typical tyrosine kinase receptor to transduce the BDNF signal. In the hippocampus of ADHD rats, such as spontaneously hypertensive rat (SHR), the expression of TrkB is decreased while treadmill exercise enhances BDNF and TrkB expressions [44].

p75

Another name of p75 receptor is low-affinity nerve growth factor receptor (LNGFR), which belongs to the family of protein growth factors. The p75 receptor is one of the roughly 25 members of the TNF receptor super family (TNFRSF) and binds all neurotrophins with similar nanomolar affinities [45]. It mainly expresses during the early stage of neuronal development and plays an important role in controlling the neuronal survival and in processing outgrowth [46].

Pathways

TrkB-Mediated Signal Pathways

BDNF/TrkB-stimulated intracellular signaling is critical for neuronal survival, morphogenesis, and plasticity. There are at least three signaling transduction pathways mediated by TrkB receptor, including phospholipase Cγ (PLCγ), mitogen-activated protein kinase/extracellular signal-regulated protein kinase (MAPK/ERK), and phosphoinositide 3-kinase (PI3K) pathways [47]. Activation of PLCγ leads to the release of calcium from the endoplasmic reticulum and to the activation of a calcium-calmodul-independent kinase II (CAMKII), ending in phosphorylation of cAMP response element-binding protein (CREB) and activation of transcription. The MAPK/ERK and PI3K pathways mainly mediate the neuronal survival effect of BDNF. The detailed roles of BDNF/TrkB pathway in the onset and progression of ADHD remained unclear. Activation of TrkB receptor had been shown to regulate the release of dopamine [48], a major disrupted neurotransmitter in ADHD. These mechanisms may be involved in the pathogenesis of ADHD; changes in BDNF signaling pathway require further study in order to elucidate the specific role of BDNF in ADHD.

p75-Mediated Signal Pathways

In contrast to TrkB receptor, the p75 mainly binds the pro-BDNF and mediates the neuronal cell death. And in the sympathetic neurons, BDNF induces the phosphorylation of c-Jun via p75 activation [49].

Functions of BDNF in Neuronal Development

BDNF and its specific receptor TrkB are abundant in the CNS, indicating their essential roles in the survival of neurons and synaptic transmission [50]. BDNF participates in the proliferation, differentiation, maturation, and survival of immature neurons and promotes the synapse formation in mature neuron [50, 51]. It is suggested that neuronal spine formation and plasticity might underlie the pathophysiology of ADHD [52]. Neuron projection morphogenesis and neuron migration pathways were implicated by gene-encoding adhesion molecules, including BDNF.

Neuronal Proliferation

Nestin immunoreactivity was reduced in the olfactory bulb of BDNF knockout mice, indicating that BDNF knockout mice

possess fewer palingenetic olfactory neurons. When added to cell cultures containing olfactory receptor neuron (ORNs) precursors, BDNF leads to a dose-dependent increase in the number of nestin-positive neurons, suggesting that BDNF may influence olfactory neuronal proliferation [53]. In the transgenic frogs, overexpressing BDNF can promote glia cell proliferation [54]. As mentioned above, BDNF plays a key role in the survival and differentiation of midbrain dopaminergic neurons [47]. A decreased midbrain BDNF activity may cause midbrain dopaminergic dysfunction, and therefore, resulting in ADHD [7].

Neuronal Migration

Several lines of evidence supported the critical role of BDNF in the neuronal migration. For example, the cerebellar granule cells from $BDNF^{-/-}$ mice were able to attach to glial fibers but failed to begin migrating while supplementing with exogenous BDNF enabling $BDNF^{-/-}$ granule cells to migrate properly [55]. Meanwhile, injection of BDNF into the lateral ventricles in embryonic mouse induced the premature initiation of migration of neurons destined for deep cortex [56]. Additionally, BDNF was shown to promote the bone marrow mesenchymal stem cell (BMSCs) migration during ischemia [57], which provided a possible therapeutic strategy for stroke.

Neuronal Differentiation

Neural stem cells (NSC) are isolated from the E2 rat cerebral cortex, cultured with BDNF for 3 days. With the immunofluorescence staining after BDNF inducing, the number of NSC differentiates into neurons in the BDNF added group and was about five times in contrast to the control group [58]. After injecting BDNF into the cerebroventricle of neonatal rats, an increase in GABA content in the striatum was observed. In BDNF-treated striatal cultures, the newly differentiated neurons extended elaborate neurites and exhibited strong glutamic acid decarboxylase (GAD) immunoreactivity, promoting a GABAergic neuron process. These observations suggested that BDNF may contribute to phenotypic differentiation of GABAergic neurons during development [59].

Neuronal Maturation

BDNF elicited significant changes in several properties of spontaneous synaptic currents (SSCs), indicative of more mature synapses in *Xenopus* nerve-muscle cocultures. Moreover, BDNF increased the levels of the synaptic vesicle proteins, synaptophysin, and synapsin 1 in the spinal neurons. These results suggested that BDNF promoted maturation of neurons to form synapse [60]. During brain development, the size of the striatum could be determined by BDNF because it supports the survival of immature striatal neurons at their origin, promotes maturation of striatal neurons, and facilitates establishment of striatal connections [61].

Synaptogenesis

BDNF modulates $GABA_AR$ phosphorylation and miniature inhibitory synaptic currents (mIPSCs) in culture and brain slices [62]. In the cocultures of the thalamus and cortex, thalamic axon branching was substantially increased after BDNF was added to the culture medium. While endogenous BDNF is removed by inhibiting TrkB expression, the number of axonal branch points was significantly reduced [63]. In the hippocampal slices from BDNF overexpression in mice, the spontaneous coactive network activity is dramatically increased, suggesting the synchronize gene expression and synaptogenesis in vast numbers of neurons were promoted by BDNF [64] via TrkB receptor in both pre- and postsynaptic cells. It is reported that in Purkinje cells, application of BDNF promotes the dendritic growth and synapse formations of inhibitory synapses via TrkB receptor too [65–67].

BDNF and ADHD

The Genetic Variation of BDNF and ADHD

Evidences from family, twins, adoption, and association studies consistently indicate that genetic factors play a substantial role in the etiology of ADHD with an average heritability of 76 % [68]. In numerous studies on genetic epidemiology of ADHD, the Val66Met polymorphism which is the only known functional mutation in BDNF has been focused mostly on.

Val66Met is located at nucleotide 196 within the 50 precursor peptide (pro-BDNF) sequence and can cause an amino acid substitution of valine to methionine at codon 66 as described above [20]. The anatomical effects of this functional variation are most apparent in the hippocampus and prefrontal cortex where there is especially abundant expression of BDNF [69, 70]. Transgenic rats with the Met allele exhibited abnormal cellular transport and secretion of BDNF in hippocampal neurons compared with the Val allele [69]. In the studies of brain morphometry, Val/Met individuals have repeatedly shown a smaller hippocampal volume compared to Val/Val controls by structural magnetic resonance imaging scans [71]. In addition, decreased volume in the Met allele carriers has been found in the dorsolateral prefrontal cortex, an area associated with planning and higher-order cognitive functions [72].

We performed a case-control study to explore whether Val66Met contributed to genetic susceptibility to ADHD in the Chinese mainland population. The cases were ADHD children recruited from Hunan Children's Hospital in Changsha city of China from June 2012 to July 2013, while the

controls were healthy children for physical examination in this hospital during the same period. Eligible cases who met the criteria were included: (1) diagnosed as ADHD by psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV [73], (2) at the age of 6–17, (3) scored 70 and above tested by China-Wechsler Intelligence Scale for Children (C-WISC) [74], (4) no acute or chronic physical infection history in the recent two weeks. And individuals with major neurological handicaps, schizophrenia, pervasive development disorder, epilepsy, mental retardation, and other brain disorders were excluded. Correspondingly, healthy children of the same age who scored 70 and above in the Wechsler intelligence test and had no any family histories of ADHD and other mental diseases were enrolled in the control group. Finally, 192 cases and 192 controls were involved in our study. This work was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology, and all the subjects' parents signed the informed consent. Genomic DNA was extracted from peripheral blood according to manufacturer's instructions (blood genomic DNA extraction kit; TIANGEN, Beijing, China). Genotyping was accomplished using the Sequenom MassARRAY genotyping platform (Supplementary Fig. 1). The results showed that there were no significant differences in the genotype (χ^2=0.857, P=0.651) and allele frequencies (χ^2=0.354, P=0.552, odds ratio (OR)=1.096, 95 % confidence interval (CI)=0.811, 1.481) of Val66Met between ADHD patients and controls (Table 1). The demographic characteristics of cases and controls were shown in Supplementary Table 1.

The failure of our first study in the Chinese mainland population to identify the Val66Met polymorphism of BDNF involved in ADHD may be due to several reasons. (1) Multiple genetic factors may be involved in complex disorders such as ADHD and might only be identified through studies in larger population. (2) The differences of studied samples in ethnicity, age, gender, and clinical phenotypes (persistence, comorbidity, etc.) might lead to different risks for ADHD. Hence, the related researches in different populations have not yet reached consistent results. For example, Kent [75] and Lanktree [37] found a significant overtransmission of the Val allele in Caucasian through family-based study (OR=1.61, 95 % CI=1.06–2.44; OR=1.83, 95 % CI=1.03–3.26, respectively), and Bergman found that the Val66Met polymorphism in BDNF gene was associated with increased hyperactive-impulsive symptom of ADHD at the age of 13–14 through a community-based cohort study (RR=1.71, 95 % CI=1.08–2.68); while Cho, Xu, et al. found no evidence of association in Caucasian and Taiwanese samples by a case-control study [76–79]. (3) Gene-gene and gene-environment interactions might have a potential impact. Therefore, the negative results in our study should not necessarily be considered a refutation of the association between BDNF and ADHD.

In addition, two studies reported an association between the C270T polymorphism and ADHD. C270T is in the 5′ noncoding region of intron 1 [78], and its functional significance has not yet been investigated. Xu [78] found a significant overtransmission of the C allele in the Taiwan population, and Aureli [80] got consistent results in Caucasian by a case-control study. Furthermore, genome-wide association studies (GWAS) which is a relatively new tool for the identification of multiple risk genes for complex disorders in a hypothesis-free manner suggested that such basic processes as neuronal migration and neuronal plasticity relevant to BDNF seemed involved in ADHD, despite no significant variants found [52, 81, 82].

BDNF and ADHD Mouse Model

Earlier studies showed that BDNF heterozygous null mutants [83] and BDNF conditional knockout mice [84] exhibit increased locomotor hyperactivity, which mimics fundamental behavioral characteristics of ADHD. Several kinds of mouse models to study the function of BDNF, including BDNF knockout [85], BDNF function-blocking antibodies [86], forebrain TrkB signaling gene knockout [87], or expression of truncated TrkB [88] all showed impaired hippocampal-dependent learning deficits in mice which is similar to the academic impairment in ADHD patients. Moreover, it is found that the loss of BDNF in broad forebrain regions in mice during early stages of development caused hyperactivity and hippocampal-dependent learning deficits, which may be attributed to its participation in the process of cognition by BDNF/TrkB pathway [89].

Table 1 Comparison of the allele frequencies of Val66Met between ADHD probands and controls

	AA	AG	GG	χ^2	P	A	G	χ^{2a}	P^a	OR (95 % CI)
Cases, *n*	43	86	55	0.857	0.651	172	196	0.354	0.552	1.096 (0.811, 1.481)
Controls, *n*	39	81	41			159	163			

[a] Chi-square value and P value adjusted for age

OR odds ratio, *95 % CI* 95 % confidence interval

BDNF and ADHD Treatment

Psychostimulants (methylphenidate, amphetamine, and pemoline) and antidepressants (tricyclic antidepressants and selective serotonin reuptake inhibitors) are commonly used drugs in the therapy of ADHD [90]. Both of them can regulate central BDNF, which could be helpful for ADHD treatment [91, 92]. The psychostimulants can also enhance the release of dopamine and norepinephrine in the midbrain through activation of the TrkB receptor which is one of the BDNF receptors [93].

It is reported that dopaminergic agonists can regulate mRNA and protein levels of BDNF [94]. Meredith et al. found that mRNA and immunoreactivity of BDNF in the basolateral amygdala, rostral piriform cortex, and paraventricular nucleus of the hypothalamus rose after repeated injections of amphetamine to rats [91]. Juvenile rodents injected methylphenidate also exhibited similar effects in hippocampal and frontal regions [95]. Moreover, it is found that the expression of BDNF was increased in the mouse striatum after a single intraperitoneal injection of methamphetamine [96]. And the behavioral response to psychostimulants enhances by exogenous infusions of BDNF in rats via increased mobilization and/or docking of synaptic vesicles to presynaptic active zones [97]. All the above research results provide evidence of a strong correlation between BDNF and ADHD treatment.

Furthermore, pharmacogenetic studies of ADHD showed a correlation between the Val66Met polymorphism of BDNF and amphetamine response [98]. Kim et al. found that ADHD children with the Val/Val genotype had a better response to osmotic release oral system-methylphenidate in Korea [99]. Flanagin's study also indicated that the activity-dependent secretion of BDNF by neurons significantly increased in the Val/Val patients than that in the Met/Met ones when treated with amphetamine [98]. Some scholars studied the role of BDNF in the nondrug therapy of ADHD (behavioral interventions, diet regimens, cognitive training, and neurofeedback) as well [100]. Rommel et al. found that exercise may improve executive functioning and behavioral symptoms associated with ADHD, and BDNF was involved in mediating these effects [101].

Future Perspective

ADHD is a common psychiatric disorder in childhood, related to abnormal brain development and function. The possible relationship of BDNF and ADHD has been extensively studied in ADHD, while how to manipulate BDNF expression and its downstream signaling is of great interest for novel therapeutics innovations to ADHD. It is because it is known that levels of BDNF are maintained within an optimal range in the brain, and the alterations of BDNF are always brain region-specific in different diseases. Simply increasing or decreasing BDNF levels may lead to abnormal neuronal excitotoxicity, undesired increased proliferation and survival of cancer cells or side effects in cardiovascular system [102]. To deliver adequate doses of BDNF to specific brain regions that can be handled and examined with predictable pharmacokinetics for adequate period is a strong challenge in the future research [103]. In order to search for more effective and applicable BDNF-based therapies, carrying out more extensive animal experiments and pharmacological studies is crucial in light of the impact of BDNF on disease processes.

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Conflict of Interest The authors declare that there are no conflicts of interest.

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