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FEATURE REVIEW

Is it time to reassess the BDNF hypothesis of depression?

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The brain-derived neurotrophic factor (BDNF) hypothesis of depression postulates that a loss of BDNF is directly involved in the pathophysiology of depression, and that its restoration may underlie the therapeutic efficacy of antidepressant treatment. While this theory has received considerable experimental support, an increasing number of studies have generated evidence which is not only inconsistent, but also directly contradicts the hypothesis. This article provides a critical review of the clinical and preclinical studies which have been responsible for this controversy, outlining pharmacological, behavioural and genetic evidence which demonstrates the contrasting role of BDNF in regulating mood and antidepressant effects throughout the brain. I will also review key studies, both human and animal, which have investigated the association of a BDNF single-nucleotide polymorphism (Val66Met) with depression pathogenesis, and detail the number of inconsistencies which also afflict this novel area of BDNF research. The article will conclude by discussing why now is a critical time to reassess the original BDNF hypothesis of depression, and look towards the formation of new models that can provide a more valid account of the complex relationships between growth factors, mood disorders and their treatment.
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Introduction

The last 50 years of depression research have been dominated by the 'monoamine hypothesis', postulating that a decrease in basal levels of serotonin, noradrenalin and possibly dopamine, may underlie the pathogenesis and maintenance of depressive symptoms.[1] However, the lack of universal efficacy and 2–3 weeks of therapeutic latency associated with monoamine potentiating antidepressants has led to the supposition that monoamine deficits may not reflect a core feature of depression pathophysiology, but are the result of neural dysfunction.[2,3] This theory has directed research away from monoamines and towards the putative role of growth factors such as brain-derived neurotrophic factor (BDNF), known to be critically involved in regulating neural structure and plasticity in the adult brain.[4,5]

The neurotrophin hypothesis postulates that a loss of BDNF plays a major role in the pathophysiology of depression, and that its restoration may represent a critical mechanism underlying antidepressant efficacy. This theory has received considerable support and led to major investigation into the potential of BDNF as a novel target for antidepressant treatment. However, this theory appears to be valid only when considered with relation to hippocampal function, with an increasing number of studies of mesolimbic BDNF providing evidence which is not only inconsistent with this theory, but also directly contradicts it. This review highlights the major advances in pharmacological, behavioural and genetic research which have unveiled the true complexity of the relationship between growth factors and emotionality, and discusses why in light of such findings, now is a critical time to reassess the BDNF hypothesis of depression.

The BDNF hypothesis of depression: the argument for

The rationale for the BDNF hypothesis originates from observations that acute and chronic stress in humans both decrease endogenous neurotrophin levels and can lead to significant atrophy of the hippocampus, a structure known to be involved in controlling emotionality.[6–8] These events may be causally linked via neurogenesis.[9] Within the last decade, it has become widely accepted that the subventricular and subgranular zones of the dentate gyrus are major sites of cell proliferation in the adult brain,[10,11] a process which appears to be involved in maintaining balanced mood.[12]

Neurogenesis requires the proficient co-ordination and regulation of cell proliferation, migration, differentiation and death, processes mediated, at least in part, by neurotrophins. BDNF promotes the survival of neurones in the central nervous system by binding

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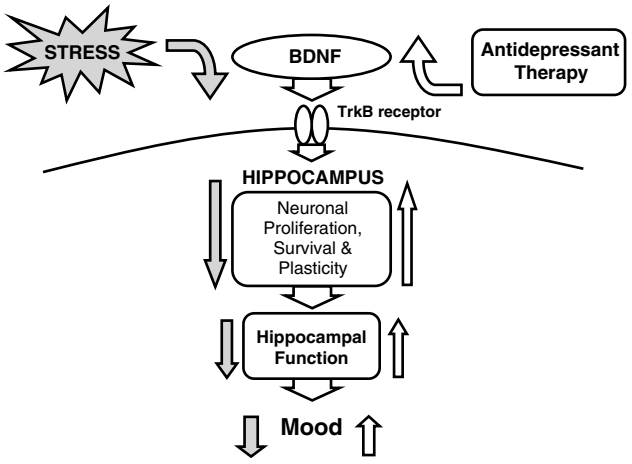

Figure 1 Simplified model outlining the opposing roles of stress and antidepressant therapy on hippocampal BDNF expression, hippocampal function, and mood. Abbreviations: BDNF, brain-derived neurotrophic factor; TrkB, tyrosine kinase receptor B.

to tyrosine kinase receptor B (TrkB) receptors on target neurones.[13] Although originally believed to support neurogenesis solely by promoting growth and proliferation, BDNF activity at the TrkB receptor also has potent neuroprotectant properties.[14] For example, activation of the mitogen-activated protein kinase pathway increases expression of bcl-2, a protein family involved in caspase-regulated apoptosis.[15] Furthermore, BDNF is able to regulate neuronal survival via the phosphatidylinositol 3-kinase (PI3-kinase)/Akt pathway. BDNF–TrkB interaction results in PI3-kinase generating phosphatidyl inositides which activate the protein kinase Akt (protein kinase B). Akt is able to phosphorylate, and therefore regulate a number of cell survival-related proteins, including IkB, the forkhead transcription factor FKHRL1, glycogen synthase kinase-3B (GSK-3B) and Bad, a pro-apoptotic member of the Bcl-2 family.[16] Therefore, it is hypothesized that precipitating factors such as chronic stress may lead to a downregulation of BDNF neurotrophic support, decreasing the anti-apoptotic regulation of bcl-2 and thus reducing neurogenic cell survival. This has detrimental consequences for hippocampal function and ultimately leads to the development of depressive symptoms (Figure 1).[17] Considerable support for this theory has been provided by both preclinical and clinical evidence.

Preclinical evidence

Diverse manipulations that induce depressive-like behaviour in rodents illustrate the ability of both physical and psychological stress to modulate endogenous BDNF expression—see Table 1.[18,19] The earliest demonstration of a relationship between stress and BDNF used an immobilization stress paradigm, involving the physical restraint of rats over an acute (8 h) or chronic (45 min/day for 7 days) time period. Both of these manipulations were found to induce significant decreases in hippocampal levels of BDNF mRNA, with greatest reductions occurring in the dentate gyrus, CA1 and CA3 pyramidal cell layers of the hippocampus.[20–23] Similar findings have been reported using alternative stressors, such as social isolation,[24] social defeat in mice,[25] chronic swim stress[26] and exposing rats to a cue paired previously with an electric shock.[27] Furthermore, a 24 h period of maternal separation leads to the emergence of a depressive-like phenotype and subnormal hippocampal BDNF expression later in adult life, as well as attenuated stress-induced BDNF alterations.[28] This suggests that a predisposition to depression caused by an early developmental insult may be mediated by a persistent impairment of the BDNF signalling pathway.

Evidence for the direct action of BDNF on emotional behaviours has been provided by experiments in which BDNF is infused directly into the midbrain, hippocampus and lateral ventricles of the rat. Antidepressant-like effects were seen in the forced swim and learned helplessness paradigms of despair, with equipotency to conventional antidepressants.[29–31] This suggests that the BDNF–TrkB pathway could represent a valid target in the development of novel antidepressant agents, which due to being downstream of synaptic monoamine modulation, may deliver superior efficacy, reduced side effects and a decreased therapeutic latency compared to currently available pharmacological treatments.

A number of investigators have studied the involvement of BDNF in the therapeutic mechanisms of antidepressant treatments. In contrast to the effects of stress, a range of pharmacological antidepressants increase both mRNA and protein levels of BDNF in various areas of the rat brain. These include monoamine oxidase inhibitors (MAOi), selective serotonin reuptake inhibitors (SSRI), noradrenalin reuptake inhibitors (NARI) and tricyclic antidepressants.[21,32–40] Importantly, the ability of these drugs to increase BDNF is dependent on chronic administration, suggesting that their mood-enhancing effects may be functionally related to chronic changes in neurotrophic activity. In addition, antidepressant strategies which do not directly target the monoamine system, such as electroconvulsive shock therapy, transcranial magnetic stimulation, exercise and the novel α-amino-3-hydroxy-5–methyl-4–isoxazolepropionic acid (AMPA) receptor potentiators and *N*-methyl-D-aspartic acid (NMDA) antagonists, also increase mRNA or protein BDNF levels in the rat brain.[21,41–49] Although the mechanisms involved in BDNF upregulation remain unknown, SSRI and NARI antidepressants have been reported to increase hippocampal levels of cyclic AMP response binding protein (CREB) in the rat, a nuclear transcription factor known to regulate BDNF expression.[32]

Clinical evidence

While animal models of depression and anxiety have provided significant insight into the potential role of

Table 1 Animal and human studies supporting the BDNF hypothesis of depression

Animal	
BDNF levels decrease in the rat hippocampus following various stressors	Exposure to cues paired previously with shocks[25] Immobilization[18–21] Maternal separation (BDNF protein[26]) Social isolation[22] Chronic swim stress (prefrontal cortex and striatum)[24]
BDNF levels decrease in the mouse hippocampus following stress	Social defeat[23,57]
BDNF levels increase in the rat hippocampus following various antidepressant treatment	AMPA potentiators[46] ECS[19,33] Exercise[31,34,43–45] (increase also found in the VTA, but not piriform cortex[37]) MAOi[19,31,33,34,39,40] (also found to increase BDNF protein[41]) NARI[35,45] NMDA antagonists[47] SNRI (low dose only, increases BDNF protein[38]) SSRI[19,45] TMS (also causes increases in parietal and piriform cortex[42]) Tricyclic[19,31,33,38,57]
BDNF levels increase in the mouse hippocampus following various antidepressant treatment	ECS (BDNF protein[58]) SSRI[35,36] Tricyclic[36]
TrkB expression is increased in the rat hippocampus following various antidepressant treatment	ECS[19] MAOi[19] NDMA antagonist[47] SSRI[19] Tricyclic[19]
BDNF provides antidepressant-like effects in the rat when administered directly into:	Hippocampus[28] Lateral ventricles[29] Midbrain[27]
Human	
BDNF and TrkB expression are decreased in depressed patients	Post-mortem hippocampal mRNA and protein[49] Serum protein from living patients[51–53,56]
BDNF levels are increased in patients receiving pharmacological antidepressants	Post-mortem hippocampal protein[48] Serum protein from living patients[53–56]

BDNF levels refer to mRNA apart from where specified.
Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; ECS, electroconvulsive shock; MAOi, monoamine oxidase inhibitor; NARI, noradrenalin reuptake inhibitor; NMDA, *N*-methyl-D-aspartic acid; SNRI, serotonin and noradrenalin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TMS, transcranial magnetic stimulation; TrkB, tyrosine kinase receptor B; VTA, ventral tegmental area.

BDNF in these disorders, clinical studies that have been vital for ensuring these findings can be extrapolated to humans. Post-mortem analysis has detected decreased BDNF and TrkB expression in the hippocampus of depressed suicide patients, and increased levels in patients medicated with antidepressants before death.[50–52] Furthermore, serum BDNF in living depressed patients is abnormally low, but can be restored following pharmacological antidepressant treatment.[53–58]

The BDNF hypothesis of depression: the argument against

When considered in isolation, the preclinical and clinical evidence outlined above appears to provide substantial support for a role of BDNF in both the pathophysiology of depression and the therapeutic mechanisms underlying its treatment. This has generated significant interest into the putative role of neurotrophins in psychiatric disorders and their potential manipulation for the development of novel antidepressant therapies. However, the proposed relationship between BDNF, depression and antidepressant action has by no means received universal support, with a considerable number of recent studies generating data which are markedly inconsistent with such a theory—see Table 2.

Pharmacological evidence against the role of BDNF in depression has been provided by Dias *et al*.[35] who report that chronic fluoxetine had no effect on exon-specific BDNF transcript levels. Furthermore,

Table 2 Animal studies which argue against the BDNF hypothesis of depression

NAc BDNF levels and depressive-like behaviour are increased in the mouse following social defeat stress.[62]
Increased hippocampal BDNF protein, as a result of communal nesting, increases depressive-like behaviour in the mouse forced swim test.[60]
The SSRI antidepressant fluoxetine has either no effect,[33] or decreases BDNF mRNA in the rat hippocampus.[59]
BDNF infusions into the VTA increase depressive-like behaviour in the rat forced swim test.[61]
Suppression of BDNF receptor TrkB expression within the VTA provides antidepressive-like behaviour in the rat forced swim test.[61]

Abbreviations: BDNF, brain-derived neurotrophic factor; NAc, nucleus accumbens; SSRI, selective serotonin reuptake inhibitor; TrkB, tyrosine kinase receptor B; VTA, ventral tegmental area.

Miro *et al*.[59] found that 14 days of chronic fluoxetine treatment actually downregulated BDNF expression in the rat hippocampus. However, Dias *et al*.[35] report an increase in BDNF following chronic electroconvulsive shock, tranylcypromine and desipramine treatment, suggesting that this negative result may be specific to serotonin modulators. It is also possible that the paradoxical downregulation of BDNF reported by Miro may be due to an insufficient dosing period, as a later study by De Foubert reports that chronic fluoxetine treatment is only able to increase BDNF to significant levels following 21 days of treatment.

There are also reports that increased levels of BDNF may cause depression. Mice reared in communal nests exhibit both increased adulthood levels of BDNF and depressive-like behaviour, as demonstrated by an increase in escape behaviour in the forced swim paradigm of behavioural despair.[60] While it is possible that the behavioural changes reflect improved learning (allowing the rats to adopt a more effective coping strategy when faced with an inescapable threat[61]), there are additional reports of increased BDNF being depressogenic. Seven days of BDNF infusions into the ventral tegmental area (VTA) have been found to reduce latency to immobility in the forced swim test, indicative of a pro-depressive effect,[61] while viral-mediated suppression of the BDNF receptor TrkB, delivered significant antidepressive-like effects.[61] This controversial finding has also been reported in a chronic social defeat model of depression. Berton *et al*.[62] show that mice exposed to 10 days of social defeat exhibit an increase in depression-like behaviour coupled with an increase in nucleus accumbens (NAc) BDNF protein levels, at both 24 h and 28 days after the original stress manipulation. Furthermore, the development of this depressive-like phenotype was blocked by viral-mediated VTA-specific BDNF repression, suggesting that an intact BDNF system in the VTA–NAc pathway is necessary for the development of depressive-like symptoms in this model.[62]

These results are in stark contrast to the original hypothesis regarding the role of BDNF in depression, suggesting that its functional properties in the VTA–NAc pathway may be the opposite of that reported for the hippocampus.[29] While there is an argument that this paradox may be an artifact of methodological variance across studies,[63] it is more likely that the complex symptomology and pathophysiology of depression is related to diverse and regionally specific neurotrophin function.[62] The human *BDNF* gene is highly complex, with eight exons, multiple splice variants and alternate polyadenylation sites providing the potential for multiple *BDNF* transcripts.[64] Nestler and co-workers[18] have already begun to explore the importance of differential transcriptional regulation for the pathogenesis of depression. Two *BDNF* transcripts (III and IV) were found to be downregulated in a mouse model of social stress. Chronic imipramine increased the expression of these transcripts by modifying histones, proteins that wrap up DNA, so that gene expression is turned off. It is thus conceivable that differential regulation of *BDNF* transcripts by stress and antidepressant treatments may result in contrasting functional effects. Further research into this theory will be critical to evaluate the potential of the BDNF signalling pathway as a valid target for novel antidepressant therapies.

Can genetically altered mice help?

Genetic manipulation of mice has been particularly useful in researching the role of BDNF in depression, enabling a progression from relatively circumstantial evidence to direct causal studies (Table 3). Complete deletion of the *BDNF* gene results in severe developmental defects and embryonic death,[65] so most research has used mice heterozygous for the *BDNF* gene, or employed conditional and inducible 'knockout' strategies. In accordance with the hypothesized role of BDNF in the pathophysiology of depression, mice with compromised BDNF signalling would be expected to exhibit either a depressive-like phenotype or an underlying vulnerability for its development. However, the behavioural profile of the heterozygous *BDNF* mouse is reported to be indistinguishable from wild-type controls in tests of locomotor activity, exploration, hedonic sensitivity and behavioural despair.[66–68] Heterozygous *BDNF* mice were shown to exhibit depressive-like abnormalities in a learned helplessness task, but the reliance of this assay on electric shocks coupled with the fact that these mice demonstrate reduced pain sensitivity suggests that these results should be interpreted with caution.[66]

A possible explanation for these negative findings is that the reduction of BDNF expression in

Table 3 Evidence for and against the BDNF hypothesis of depression from studies using genetically altered mice

Evidence for
Heterozygote *BDNF* mice exhibit a decreased response to the behavioural effects of tricyclic antidepressants.[73]
Mice over-expressing BDNF exhibit decreased depressive-like behaviour in the forced swim test.[78]
Conditional *BDNF* knockout mice show depressive-like behaviour in the tail suspension test.[72]
Evidence against
Heterozygous *BDNF* mice do not exhibit depressive-or anxiety-like behaviour.[66–68]
Male conditional *BDNF* knockout mice do not exhibit depressive-like behaviour in the forced swim and sucrose preference tests[72] (although females do[73]).
BDNF TrkB receptor knockout/non-functional mice do not exhibit depressive-like behaviour in the forced swim test, or anxiety-like behaviour in tests of neophobia and plus maze.[67,75]
Mice over-expressing BDNF exhibit increased anxiety-like behaviour and pathology.[78]

Abbreviations: BDNF, brain-derived neurotrophic factor; TrkB, tyrosine kinase receptor B.

heterozygote knockouts may not be sufficient to induce spontaneous depressive-like behaviour, or that the constitutive reduction in BDNF during embryonic development has led to the induction of compensatory mechanisms. These limitations have been minimized by the utilization of conditional knockout technology. Using a cre-loxP recombination system, the *BDNF* gene can be deleted in the forebrain of mice 14–21 days after birth, consequently terminating BDNF activity and eliminating the potential confounds inherent of conventional knockout approaches.[69–71] These mice have been reported to exhibit depressive-like behaviour in the tail suspension test, an additional behavioural despair paradigm[72]. However, the same mice also exhibited a marked antidepressive-like phenotype in the forced swim test.[72] Monteggia *et al*.[73] report that female, but not male, conditional *BDNF* knockout mice exhibit depressive-like behaviour in the forced swim and sucrose preference test of anhedonia. Furthermore, both male and female mice were found to exhibit a decreased response to the behavioural effects of the tricyclic antidepressant desipramine. While this study provides support for the role of BDNF in the mechanisms of antidepressant treatment and replicates epidemiological findings of sexual dimorphism in depression vulnerability,[74] the lack of a depressive phenotype in male mice adds to the inconsistencies surrounding the proposed critical role of BDNF in mood regulation. Furthermore, the rewarding and hedonic properties of sucrose assessed in this study are likely mediated by the mesolimbic system including the VTA and NAc. With regard to the paradoxical effect of BDNF in the VTA and hippocampus,[62] mice suffering reduced expression of BDNF might actually be expected to exhibit an increase in hedonic response, rather than the decrease reported by Monteggia *et al*.[73]

A complementary approach to decreasing BDNF levels is to reduce the expression of its receptor TrkB. Knocking out forebrain-specific TrkB receptors or overexpressing the non-functional truncated form has been shown to have no effect on depressive- or anxiety-like behaviour in mice, as shown by normal levels of immobility in the forced swim test, normal elevated zero maze activity and unaltered neophobia.[67,75]

The results from these genetically altered mice are clearly incongruous with the original hypothesis of BDNF function in depression, demonstrating that a reduction in BDNF activity is not sufficient to induce clear depressive- or anxiety-like symptoms. Duman and Monteggia argue that 'the behavioral paradigms used for these studies are probably not true models of depression and may therefore not reveal the effects of certain gene manipulations on mood'.[76] While it is a valid point that the forced swim test, used in a majority of such studies, suffers considerable limitations in terms of construct and face validity, the authors fail to mention these limitations when the same paradigm has been cited in support of their neurotrophic hypothesis.[30,76] Studies utilizing alternative assays, such as novelty-induced hypophagia and chronic social defeat,[18,77] will be important in determining the strength of this argument. Furthermore, while a loss of BDNF may not generate spontaneous depressive traits, it may represent a predisposing factor, and a manipulation such as chronic stress is necessary for its manifestation and subsequent detection. This approach has not yet been explored.

An additional method of investigating the role of BDNF in mood regulation has been to assess the behavioural and cellular effects following its overexpression. Govindarajan *et al*.[78] reports that mice genetically modified to overexpress BDNF exhibit increased anxiety-like behaviour as well as an increase in spinogenesis of the basolateral amygdala, comparable to that seen in wild-type mice exposed to chronic immobilization stress. Furthermore, the same stress protocol was unable to exacerbate the cellular abnormalities in the transgenic mice, suggesting a role for BDNF in stress-induced plasticity of the amygdala. On the basis of the comorbidity of anxiety and depression, it is often assumed that these disorders must share a similar pathophysiology. If this is true, these results would provide additional evidence against a causal relationship between reduced brain BDNF levels and depression. However, Govindarajan *et al*.[78] also report that overexpression of BDNF was able to protect mice from stress-induced atrophy of

hippocampal CA3 pyramidal neurones as well as decreased immobility in the forced swim test, both indicative of decreased susceptibility to depression. These results clearly demonstrate the importance of acknowledging the dissociations between depression and anxiety, such as the possible regionally specific role of BDNF in their pathology as well as ensuring the most valid behavioural models are used for their assessment. A note of caution while interpreting these results is the ethological validity of such genetic overexpression. The 8- to 12-fold increase in BDNF protein expressed by these mice is unlikely to occur in the normal brain, thereby limiting the extent to which this animal can inform on genuine physiological conditions.

Could a single-nucleotide polymorphism be the answer?

The role of BDNF in depression has also been investigated by determining the association between gene-encoding variants and behaviour in large-scale human population studies. While no specific depression-associated genes have yet been identified, it is estimated that 40–50% of depression vulnerability has a genetic component.[74,79,80] One approach employed in this area of research is the mapping of gene variations to specific behavioural traits across large numbers of either normal or clinical populations. One such trait is neuroticism.[81,82] Large population-based twin studies have found a substantial genetic correlation between neuroticism and depression[83–85] and consequently it has been used as a marker for depression vulnerability.[86–91] Sen *et al*.[92] investigated a putative association between depression vulnerability and a single-nucleotide polymorphism in the 5′ pro-domain of *BDNF*, which results in an amino-acid substitution of valine (Val) to methionine (Met) at codon 66 (Val66Met). The authors report that in a sample of 441 Caucasian American subjects, the Val allele was associated with higher neurotic scores, suggesting a positive relationship between this *BDNF* gene polymorphism and depression.[92] The authors conclude that the Met allele may be associated with increased activity or greater efficiency of BDNF processing and, in line with the BDNF hypothesis, 'protective' against depression. This finding is supported by a similar study in a population of 343 German subjects that identified higher levels of trait anxiety, a co-morbid factor of depression, in individuals carrying a Val/Val genotype compared with Val/Met or Met/Met subjects.[93] In contrast, three recent studies from Chinese and Korean populations have reported no association between this *BDNF* polymorphism and depression.[94–96] While such negative results could be due to underpowered sample sizes and differences in subject ethnicity,[93] recent studies carried out using much larger samples, using tens of thousands of subjects, have failed to confirm the association.[97,98] It should be noted however, that even for the most widely studied genetic variants associated with depression and anxiety, such as the serotonin transporter, meta-analyses have reported inconclusive findings, identifying a significant lack of inconsistency across studies.[99]

Despite the negative findings from genetic association studies, the presence of a relatively common and potentially functional polymorphism in the *BDNF* gene has attracted much interest. The polymorphism has been shown to be associated *in vitro* with alterations in BDNF packaging, trafficking and secretion.[8,100] Chen *et al*.[101] have provided *in vivo* evidence in support of the role of this single-nucleotide polymorphism in depression pathogenesis, reporting that mice homozygous for a Val/Met substitution ($BDNF^{MET/MET}$) exhibit a significant decrease in biologically relevant BDNF release, an increase in anxiety-like behaviour and an attenuated anxiolytic response to chronic fluoxetine. These findings provide additional support for a link between a *BDNF* single-nucleotide polymorphism, behaviour co-morbid with depression and possibly SSRI resistance. However, the conclusion that it is an increase in Met as opposed to Val expression which is associated with depression vulnerability, argues directly against the hypothesized 'protective' role of Met, as proposed by Sen *et al*.[92] This has also been reported in a number of human studies, with the Met allele most associated with increased risk avoidance behaviour (a measure of anxious temperament)[102] and showing greatest expression in individuals suffering from anxiety disorders and depression.[102,103] It has also been reported that Met expression is not associated with the development of depression *per se,* but with clinical features such as psychosis and suicidal behaviour.[104] However, others have found no such associations (Table 4).[103]

Conclusion

Evidence for the involvement of BDNF in the pathophysiology of depression is currently inconsistent. On the one hand, decreased BDNF levels are associated with both human depression and a range of rodent models of the disorder. A number of clinically effective antidepressants increase BDNF levels, while direct BDNF infusions and genetic overexpression demonstrate antidepressant-like activity. On the other hand, a number of pharmacological studies have generated negative results, while others describe findings directly contradicting a simple causal relationship between total brain BDNF levels and mood. The lack of spontaneous depressive phenotype in *BDNF* knockout mice, negative results from large-scale population studies and contradictory conclusions regarding gene polymorphisms further weaken the BDNF hypothesis of depression.

So how can such inconsistency be explained? One hypothesis has been put forward by Castren, who suggests that BDNF may act as a 'critical tool' in modulating activity-dependent plasticity within emotional processing networks, the integrity of which

Table 4 Evidence for and against an association between the *BDNF* Val66Met polymorphism and depression

Evidence for—Val
Val allele associated with higher neurotic scores in 441 Caucasian American subjects[92] and higher anxiety scores in 343 German subjects.[93]

Evidence for—Met
Met allele associated with increased risk avoidance in 208 Caucasian subjects.[102]
Increased Met allele expression in 110 depressed elderly Chinese subjects.[103]
Met allele associated with expression of suicidal and psychotic symptoms in 154 depressed Japanese subjects.[104]
Mice homozygous for the *BDNF* Met allele exhibit a decrease in biologically relevant BDNF release, an increase in anxiety-like behaviour and an attenuated anxiolytic response to chronic fluoxetine.[101]

Evidence against
No association found between *BDNF* Val/Met polymorphism and depression in samples of 192[94] and 152[95] Chinese, and 83 Korean[96] depressed patients.
No association found between *BDNF* Val/Met polymorphism and neuroticism in a sample of 7389[97] and 88142 European subjects.[98]

Abbreviations: BDNF, brain-derived neurotrophic factor; Met, methionine; Val, valine.
Val/Met refers to a single-nucleotide polymorphism in the 5′ pro-domain of BDNF which results in an amino-acid substitution of valine (Val) to methionine (Met) at codon 66.

may be compromised in depression. The physiological function of such plasticity as well as the extent to which it is modulated may determine the magnitude, and importantly the direction, of the impact BDNF levels have on mood.[105] Given the contrasting behavioural consequences of changes in neuronal plasticity within the hippocampal–prefrontal and mesolimbic pathways,[106] this hypothesis may go some way to explain the paradoxical effects of BDNF within regions of the hippocampus, NAc–VTA pathway and amygdala. While experimental support will be needed to validate Castren's ideas, the proposal of such theories, which are able to look beyond the traditional neurotrophin hypothesis and towards a more dynamic and divergent role for BDNF in mood regulation, should certainly be encouraged.

The relationship between BDNF and depression pathophysiology remains unclear, yet the studies outlined in this review demonstrate almost universal support for a role of BDNF in antidepressant treatment. The relatively focussed expression of BDNF to the hippocampus combined with its integral role in neurogenic regulation suggests that the BDNF-TrkB system may represent a valid and highly effective target for the development of novel antidepressant treatments, an approach that will undoubtedly benefit from research into *BDNF* transcription and chromatin remodelling. However, while the need for such novel therapies might remain high, it is imperative that a greater understanding of the complex and apparently dichotomous effects of BDNF manipulation across different brain regions is first acquired.

In conclusion, the many irregularities and inconsistencies identified in this article suggest that the BDNF hypothesis of depression, as it currently stands, needs to be reassessed. Like the monoamine hypothesis proposed over 40 years ago, we may have to accept that the role of BDNF lies more in the genesis of depressive symptoms than at the core of disease pathophysiology. However, the numerous limitations associated with current antidepressant treatments suggest that while it may not lead to a 'miracle cure', continued research into the antidepressant potential of neurotrophin modulation is clearly warranted.

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