BRAIN RESEARCH 1586 (2014) 162–172

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Review

Brain derived neurotrophic factor: Epigenetic regulation in psychiatric disorders

Cathy Mitchelmore[a,*], *Lene Gede*[b]

[a]*Department of Science, Roskilde University, 4000-Roskilde, Denmark*
[b]*Applied Human Molecular Genetics, Kennedy Center, Glostrup, Denmark*

ARTICLE INFO

Article history:
Accepted 30 June 2014
Available online 16 September 2014

Keywords:
BDNF
DNA methylation
Histone modifications
Neuronal plasticity
Depression
Schizophrenia
Bipolar disorder
Borderline personality disorder

ABSTRACT

Brain Derived Neurotrophic Factor (BDNF) is a neurotrophin with important functions in neuronal development and neuroplasticity. Accumulating evidence suggests that alterations in BDNF expression levels underlie a variety of psychiatric and neurological disorders. Indeed, BDNF therapies are currently being investigated in animal models and clinical studies. However, very little is currently known about the mechanisms that deregulate *BDNF* gene expression in these disorders. The *BDNF* gene structure and tissue expression pattern is complex, controlled in humans by 9 different gene promoters. Recently, epigenetic changes at the *BDNF* gene locus have been proposed to provide a link between gene and environment. In this review, we will summarize the current knowledge of *BDNF* epigenetic regulation with respect to psychiatric disorders and describe how this information can be applied in therapy and future research.

Contents

1. Introduction . . . 163
2. Human BDNF gene regulation . . . 163
   2.1. Complex gene structure and expression . . . 163
   2.2. Transcriptional regulation . . . 164
3. Epigenetic regulation of BDNF in psychiatric disorders . . . 164
   3.1. Epigenetics – a link between gene and environment . . . 164
   3.2. A role for epigenetic regulation of BDNF in psychiatric disorders? . . . 166
   3.3. Research challenges and limitations . . . 167
4. Perspectives for BDNF therapy in psychiatry . . . 169
5. Conclusion . . . 169
References . . . 170

*Corresponding author.
E-mail address: mitch@ruc.dk (C. Mitchelmore).

http://dx.doi.org/10.1016/j.brainres.2014.06.037

1. Introduction

The neurotrophin family consists of 4 members with important functions during nervous system development and neuronal plasticity. Of these, BDNF has the most abundant and widespread expression in the mammalian brain (Murer et al., 1999; Pruunsild et al., 2007). BDNF is released from neurons both pre- and postsynaptically, either constitutively or in an activity-dependent manner (Lessmann and Brigadski, 2009). Secreted BDNF can interact with two receptors: the p75 neurotrophin receptor (p75NTR) and the tropomyosin-related kinase receptor B (TrkB). Signaling by BDNF depends on the proteolytical cleavage of a pro-form of BDNF to a mature form. Whereas proBDNF binds preferentially to p75NTR, mediating apoptosis and long-term depression, mature BDNF binds to TrkB and stimulates downstream signaling pathways leading to a plethora of effects: neuronal differentiation, outgrowth of neurites, increased cell survival and strengthening of synapses (Barker, 2009; Lu et al., 2005). Due to its role in neurogenesis and long term potentiation, BDNF signaling in the limbic structures and cerebral cortex is central for learning and memory (Cunha et al., 2010).

Disruption of BDNF signaling in the brain, mainly due to decreases in expression or release, has been linked in recent years to a range of psychiatric and neurological disorders (Balaratnasingam and Janca, 2012). A polymorphism in the coding region for the prodomain of BDNF, called Val66Met, is associated with memory impairment in humans (Baj et al., 2013; Egan et al., 2003; Hariri et al., 2003). In vitro studies suggest that the polymorphism leads to decreased BDNF release (Chen et al., 2004; Egan et al., 2003). BDNF replacement therapy is actively being pursued in human and animal models of diseases, including Huntington's disease, Alzheimer's disease and depression (Nagahara and Tuszynski, 2011). Furthermore, antidepressant treatment has been shown to increase levels of serum BDNF in depressed patients (Dwivedi, 2009).

Due to the central role of BDNF in brain development and plasticity, early environmental effects on BDNF levels may have long-term effects on brain activity. Indeed, it is well known that childhood trauma can lead to psychiatric disorders in adults and that *BDNF* gene expression is reduced by acute and chronic stress, as covered by recent reviews (Balaratnasingam and Janca, 2012; Boulle et al., 2012). The mechanism leading to *BDNF* gene down-regulation is, however, currently unclear. Recent work in rodents suggests an epigenetic mechanism whereby environmental effects – such as fear conditioning, electroconvulsive seizure, early-life adversity and drug treatment – are associated with a change in *Bdnf* gene expression (Boulle et al., 2012; Roth and Sweatt, 2011). This review will focus on the human *BDNF* gene and highlight research results from recent studies of the epigenetic regulation of *BDNF* in human subjects.

2. Human BDNF gene regulation

2.1. *Complex gene structure and expression*

The human *BDNF* gene locus is complex, consisting of 11 exons and 9 different promoters (Pruunsild et al., 2007) (Table 1). Additional complexity is present due to alternative splice sites in exons II and IX, and two alternative polyadenylation sites in exon IX. The coding region for mature BDNF is in exon IX, which is present in all splice forms. Start codons for translation are present in exons I, VII, VIII and IX, leading to variations in the N-terminal signal peptide sequence of the corresponding pre-proBDNF forms. Furthermore, an antisense transcript is synthesized from the opposite DNA strand and may regulate *BDNF* transcript levels (Modarresi et al., 2012; Pruunsild et al., 2007).

Whereas all human *BDNF* alternative mRNA transcripts are highly expressed in the brain, some are also expressed in non-neuronal tissue (Pruunsild et al., 2007). For example, expression of exon I-containing transcripts is also high in the testis. Transcripts containing exons Vh, VI and IX have a widespread expression in peripheral tissues, whereas transcripts containing exons II, III, IV, V and VII are predominantly brain-specific (Table 1). Expression of *BDNF* transcripts in the human prefrontal cortex peaks in the first few years of life, consistent with

Table 1 – Characterization of the human *BDNF* gene locus.

Exon	Promoter[a]	CpG island[b]	ATG[a]	Tissue expression[a]	In vivo induction[c]	In vitro induction[d]
I	Yes	Yes	Yes	Brain and testis	Highest	Highest
II	Yes	Yes		Brain only		
III	Yes			Mainly brain-specific		
IV	Yes	CpG-rich		Mainly brain-specific	Highest	Highest
V	Yes			Mainly brain-specific		
Vh	Yes			Brain and few other tissues		
VI	Yes	Yes		Widespread		
VII	Yes		Yes	Brain only		
VIII			Yes			
VIIIh						
IX	Yes		Yes	Widespread	Highest	

Vh and VIIIh are specific to the human *BDNF* gene.
[a] Data from Pruunsild et al. (2007).
[b] Data from Boulle et al. (2012).
[c] Data from Koppel et al. (2009).
[d] Data from Pruunsild et al. (2011).