Progress in Neuro-Psychopharmacology & Biological Psychiatry 56 (2015) 122–128

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Review article

The role of neurotrophins in bipolar disorder

Gustavo Scola [a,b], Ana Cristina Andreazza [b,c,*]

[a] Department of Psychiatry, University of Toronto, 1 King's College Circle, Toronto, ON, M5S 1A8, Canada
[b] Centre for Addiction and Mental Health, 250 College Street, Toronto, ON, M5T 1R8, Canada
[c] Department of Pharmacology and Department of Psychiatry, University of Toronto, 1 King's College Circle, Toronto, ON, M5S 1A8, Canada

ARTICLE INFO

Article history:
Received 26 June 2014
Received in revised form 25 August 2014
Accepted 26 August 2014
Available online 2 September 2014

Keywords:
Bipolar disorder
Glial cell line-derived neurotrophic factor
Insulin-like growth factor-1
Neurotrophins
Vascular endothelial growth factor

ABSTRACT

Bipolar disorder (BD) is a chronic psychiatric illness of which the pathophysiology remains partially unknown. Abnormalities of neurotrophins and other trophic factors orchestrate important alterations which could be implicated in the etiology of BD. Therefore, the main objective of this review is to examine the recent findings and critically evaluate the potential role of neurotrophins that may allow us to substantially improve the development of novel treatments. The most recently published findings highlight that brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1) and vascular endothelial growth factor (VEGF) present distinct patterns in the different stages of BD, suggesting their potential in the identification of the BD subgroups and may ultimately advance treatment strategies.

Contents

Abbreviations: BD, bipolar disorder; BDNF, brain derived neurotrophic factor; CNS, central nervous system; ERK, extracellular signal-regulated kinase; GDNF, glial cell line-derived neurotrophic factor; GFRalpha-1, GDNF family receptor alpha 1; GSK3, glycogen synthase kinase-3; IGF-1, insulin-like growth factor; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NGF, growth factor; NT-3, NT-4/5, neurotrophins-3-4/5; NTs, neurotrophins; $p75^{NTR}$, p75 neurotrophin receptor; PI-3 K, phosphatidylinositol 3-kinase; SNP, single nucleotide polymorphism; TNF, tumor necrosis factor; TrK, TrK tyrosine kinase receptors; VEGF, vascular endothelial growth factor.

* Corresponding author at: University of Toronto, Medical Science Building, Room 4204, 1 King's College Circle, Toronto, ON, M5S 1A8. Tel./fax: +1 416 978 6042.
E-mail addresses: gustavo.scola@utoronto.ca (G. Scola), ana.andreazza@utoronto.ca (A.C. Andreazza).

1. Introduction

Bipolar disorder (BD) is a complex illness that presents many molecular and morphological alterations suggestive of impairment in cellular plasticity and resilience (Frey et al., 2013). As consistently reported in post-mortem studies, these modifications are generally associated with the disruption of distinct subregions and functions of the brain, one of which is the deregulation of neurotrophins (NTs) (Mufson et al., 1999). These factors that regulate cell dynamics are expressed in

http://dx.doi.org/10.1016/j.pnpbp.2014.08.013
0278-5846/

the brain in a region-specific manner and in the peripheral tissues as well. In addition to this, NTs are also capable of signaling neurons, glial cells and other cellular systems to enable survival, differentiation and growth (Huang and Reichardt, 2001; Kaplan and Miller, 2000; Mufson et al., 1999). Interestingly, these factors are primarily regulated during development and continue to be expressed in different structures of the adult brain. For example, NTs demonstrate the ability to stimulate hippocampal neurogenesis in the mature brain (Huang and Reichardt, 2001; Kaplan and Miller, 2000; Mufson et al., 1999). Several studies have been conducted using different samples such as plasma, serum and post-mortem brain tissues. The differences between these biofluids or tissues could provide independent information regarding the different levels of trophic factors and may assist in the understanding of the pathophysiology of the disorder. Taking these variations in consideration, we aimed to compile a review with the major findings regarding the alterations in the profile of NTs in BD and critically analyze the findings. The relationship between the effects of these factors and the cellular responses in BD may allow us to substantially improve the development of novel treatments.

2. Neurotrophins: general description

Among the processes and messengers involved in the regulation of cellular dynamics, such as cellular proliferation, differentiation, and growth, a group of specific proteins called NTs has received massive attention due to their crucial involvement in the maintenance of brain function (Huang and Reichardt, 2001; Kaplan and Miller, 2000; Mufson et al., 1999). Various NTs are expressed in the brain and possess specific abilities to mediate functional and structural changes in central and peripheral connections, such as synaptic function (regulating neurotransmitters and ion channels) and plasticity. Moreover, these factors play important roles outside the central nervous system (CNS), for example, in the maintenance of immune cells and cardiac development (Sariola, 2001).

The nerve growth factor family of neurotrophins including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and neurotrophins-3-4/5 (NT-3, NT-4/5) promote changes in cellular responses after binding to two specific types of cell surface receptors, the TrK tyrosine kinase receptors and the p75 neurotrophin receptor ($p75^{NTR}$), a distant member of the tumor necrosis factor (TNF) receptor family (Chao, 1994). The effects of other trophic factors, such as glial cell line-derived neurotrophic factor (GDNF), insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) will also be explored in this review. Moreover, these trophic factors bind to different receptors from the nerve growth factor family of NTs but exert their regulation of cellular effects in a similar manner. Their mechanisms of action are also described in this review.

The TrK receptor family, TrKa, TrKb and TrKc has a high-affinity for mature neurotrophins and mediates the trophic effects of the NGF family. More specifically, NGF activates TrKa, BDNF and NT-4/5 recognize TrKb, and finally, NT-3 binds to TrKa, TrKb, and Trkc with a higher affinity for TrKc (Huang and Reichardt, 2001; Kaplan and Miller, 2000). In addition, GDNF has also been shown to activate TrK receptors (Huang and Reichardt, 2001). Through these receptors, different NTs activate specific signaling pathways that induce the suppression of apoptotic proteins such as cdc-42/ras/rho G protein families, phosphatidylinositol 3-kinase (PI-3K) and activate anti-apoptotic proteins such as the mitogen-activated protein kinase (MAPK) pathway. Overall, these pathways are vital for cell survival, development, growth and synaptic plasticity. For more information regarding TrK regulation, refer to Huang and Reichardt (2001).

Moreover, each NT can also bind to the neurotrophin $p75^{NTR}$ receptor which possesses a low-affinity for mature NTs. Following the interaction between NT and $p75^{NTR}$, the TrK receptor family exhibits reduced responsiveness to NTs. The role of $p75^{NTR}$ is still unclear; however, it is believed that the activation of this receptor could lead to disruption of axonal growth and programmed cell death in neurons (Huang and Reichardt, 2001; Kaplan and Miller, 2000). $p75^{NTR}$ is believed to mediate several signaling mechanisms through the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), which potentiates TrK activity (Kaplan and Miller, 2000) and the activation of Jun Kinase, p53 and Bax induces apoptosis (Huang and Reichardt, 2001; Kaplan and Miller, 2000).

3. Neurotrophins, trophic factors and bipolar disorder

Numerous studies have shown the importance of the effects of NTs in stress response and the progression of mood disorders. BDNF is one of the most studied and abundant NTs in the brain, which is significantly reduced in the serum of patients with BD (Frey et al., 2013). In addition to BDNF, other neurotrophic factors such as NGF, NT-3 and NT-4/5 may orchestrate a global response in the pathophysiology of BD when present in imbalanced levels. Members of other families of proteins that regulate survival and development in the central nervous system (CNS), such as GDNF, IGF-1 and VEGF were found to be deregulated and may also play an important role in BD.

With this description in mind, we aimed to provide an overview of current findings regarding the effects of NTs and other trophic factors in BD. The first section focuses on the effects of the NGF family, while the second describes the properties of GDNF, IGF-1 and VEGF. The molecular mechanisms of each trophic factor and experimental findings regarding the effects of medication were also included in this review. In addition, all data was summarized in Table 1.

4. Neurotrophins

4.1. Nerve growth factor (NGF)

In the brain, NGF promotes protection of sympathetic and cholinergic neurons in the hippocampus and neocortex against programmed cell death and neurodegeneration (Freeman et al., 2004; Nguyen et al., 2010). Importantly, NGF is not only formed in the brain but can be produced in different peripheral cell types such as fibroblasts, suggesting that NGF does not reflect brain-tissue concentrations. Additionally, this NT displays important effects on stimulating axonal growth, learning and memory (Goldberg and Chengappa, 2009). Similarly to BDNF, NGF binds to the $p75^{NTR}$ and to the high affinity nerve growth factor receptor (TrKa). Once NGF is bound to TrKa, the second messengers of the PI-3K/Akt-glycogen synthase kinase-3 (GSK3) pathway are activated (Jones et al., 2003). In general, this pathway is responsible for signal transduction processes, cell survival, proliferation, differentiation, and intracellular trafficking and, has been markedly associated with the pathophysiology of BD (Jones et al., 2003; Kim et al., 2013).

However, the role of this NT remains unclear in the pathophysiology of BD as there are few studies that specifically evaluate its effects in BD, some with conflicting results. Barbosa et al. reported that NGF was decreased in the serum of patients with BD in the manic stage when compared to euthymic patients and healthy controls (Barbosa et al., 2011a). More recently, a study stated no significant differences in serum NGF levels between manic patients with bipolar I disorder and healthy controls in a baseline analysis (Kim et al., 2013). Rybakowski et al. (2013) also investigated the levels of NGF in depressed BD patients resistant and not resistant to treatment with antidepressants after a single infusion of ketamine and found no significant differences between the groups (Rybakowski et al., 2013). Despite the fact that NGF was the first NT to be identified, there is very little evidence about its potential role in the pathophysiology of BD.

4.2. Brain-derived neurotrophic factor (BDNF)

As mentioned earlier, BDNF plays an important role in the regulation of neuronal development as well as in learning and memory (Poo,