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Recent insights into antidepressant therapy: Distinct pathways and potential common mechanisms in the treatment of depressive syndromes

Dietrich van Calker[a,b,*], Tsvetan Serchov[a], Claus Normann[a], Knut Biber[a,c]

[a] Department of Psychiatry and Psychotherapy, University Medical Center, Faculty of Medicine, University of Freiburg, Hauptstrasse 5, 79104 Freiburg, Germany
[b] Department of Forensic Psychiatry, Institute of Forensic Medicine, University of Bern, Falkenplatz 18, 3012 Bern Switzerland
[c] Department of Neuroscience, Section Medical Physiology, University of Groningen, University Medical Center Groningen, 9713 AV Groningen, The Netherlands

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ABSTRACT

There is an urgent, unmet clinical need for faster and more efficient antidepressant drugs with higher response rates. In animal models of depression it was shown in the last few years that inhibition of three signaling molecules (BDNF, p11 and Homer1a) prevents efficacy of antidepressant therapy. These data not only show the crucial role of these factors for the treatment of depression, but may also point towards a better understanding of the molecular changes responsible for successful antidepressant therapy. Reviewing the literature concerning BNDF, p11 and Homer1a we here describe a molecular network in which these molecules interact with each other finally leading to facilitation of AMPA receptor signaling and plasticity, corroborating the current idea of AMPA receptors being a promising drug target in depression.

1. Introduction

Major depression is estimated to affect more than 300 million people worldwide and is associated with high individual suffering, increased risk of suicide and an enormous economic burden for the society (Eaton et al., 2008; Mrazek et al., 2014). Depressive symptoms are most likely the final common pathway of a multitude of different pathological processes triggered in the brain by stressful events (acute, chronic or early-life stress) or immunological and psychological challenge through a somatic disease. Hypotheses on the neurobiology of depression include alterations in various mechanisms such as e.g. neuroplasticity, neurogenesis and neuroimmunological regulation, the relative impact of which may depend on the specific individual disposition. Furthermore, there is an important effect of psychosocial factors, such as the living conditions, on the efficacy of antidepressant medication (Branchi, 2011; Chiarotti et al., 2017). Other factors such as early changes in emotional and social processing induced by neuropsychological factors may also modify the efficacy of antidepressant treatment (Harmer et al., 2017). It has even be argued that depression is not an illness in the classical meaning, but rather a condition formed by a network of related but independent symptoms, the dynamics of which may vary with particular contextual influences and should thus be analyzed by network analysis techniques (Bosboom and Cramer, 2013; Fried et al., 2015). While research on alterations by antidepressant therapy in serotonergic and noradrenergic neurotransmission has dominated the field for years, newer targets have been described in the last few years. These include e.g. FK506 binding protein (FKBP) 51, a co-chaperone regulating the glucocorticoid receptor, which was found important in the pathogenesis and treatment of stress-related disorders such as depression (Fries et al., 2017; Zannas et al., 2016). Equally important for the regulation of stress-dependent behavior are the corticotropin-releasing factor (CRF) gene and the central expression of CRF receptor protein in determining an individual's risk of developing depression (Waters et al., 2015). Potentially involved in the pathophysiology of depression is also the P2RX7 gene polymorphism rs2230912, a polymorphism of the gene for the P2 × 7 receptor which regulates the activity of ion channels in the neuronal membrane. The reliability of these latter findings is, however, controversial (Feng et al., 2014; Czamara et al., 2017). Very recent results have demonstrated a role for voltage activated Ca^{2+} channels in the treatment of depression. Selective serotonin reuptake inhibitors (SSRIs) directly inhibit these channels; resulting in an inhibition of stress-induced facilitated long-term depression (LTD) and depressive behavior even in the absence of the serotonin transporter in SERT-KO mice (Normann et al., 2017).

The goal of the present publication is not to compare and discuss all these various pathophysiological possibilities and mechanisms of antidepressant therapy, but rather to find biochemical actions that are common to various different treatments and may therefore provide clues to final mechanisms shared by various types of depressive syndromes and their treatment. Thus, not only classical antidepressant

* Corresponding author.
E-mail address: dietrich.calker@uniklinik-freiburg.de (D. van Calker).

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drugs, but also ketamine, electroconvulsive therapy (ECT) and sleep deprivation (SD) have been shown to increase brain levels of i) brain derived neurotrophic factor (BDNF) (Bjorkholm and Monteggia, 2016) ii) p11 (Svenningsson et al., 2013) and iii) Homer1a (Serchov et al., 2016). In the following article we will briefly present the basic characteristics of each of these different targets of treatment, discuss the pertinent potential mechanisms of action and finally examine how these targets might interact in successful antidepressant therapy.

2. The role of brain derived neurotrophic factor (BDNF) in antidepressant therapy

BDNF is one of the best studied neuronal growth factors with an important role in adult neurogenesis, neuronal maturation and synaptic plasticity. It has been implicated in several neuropsychiatric diseases including e.g. schizophrenia and autism, but its major role is believed to be in depression treatment. Since this function of BDNF has been comprehensively reviewed recently (Bjorkholm and Monteggia, 2016) we will limit our discussion to some selected aspects pertinent to our question of common and distinct mechanisms. BDNF is synthesized pre- and postsynaptically in neurons, but also in non-neuronal cells such as microglia (Song et al., 2017). Its synthesis in neurons is regulated by neuronal activity via Ca^{2+} influx through N-Methyl-D-aspartate (NMDA) receptors and voltage gated Ca^{2+} channels but in addition also by epigenetic changes (Boulle et al., 2012). Effects of BDNF are mediated by the tropomyosin receptor kinase B (TrkB) receptors which enhances synaptic efficacy via pre- and postsynaptic mechanisms. A role of BDNF in antidepressant effects is concluded from the findings that classical antidepressant drugs, ketamine, as well as ECT, enhanced BDNF and TrkB mRNA in the hippocampus and cortex and that infusion of BDNF protein into hippocampal areas in rodents induced antidepressant-like effects. In fact, there is evidence to suggest that BDNF-TrkB signaling is indeed crucial for responses to conventional antidepressants, as well as ketamine and ECT in preclinical animal models (Bjorkholm and Monteggia, 2016; Castren, 2014; Castren and Kojima, 2017; Lepack et al., 2016, 2014). That BDNF is necessary for the effect of ketamine is evident from the fact that ketamine-mediated antidepressant behavioral responses are blocked in inducible forebrain specific BDNF- and conditional TrkB knockout mice (Autry et al., 2011; Liu et al., 2012). Furthermore, infusion of a BDNF-neutralizing antibody into the medial prefrontal cortex (mPFC) abolishes ketamine's antidepressant-like effects (Lepack et al., 2014). Very recent findings suggest that ketamine's antidepressant action is mediated by ketamine induced differentiation of doublecortin-positive adult hippocampal neural progenitors into functionally mature neurons, a process requiring TrkB-dependent extracellular signal-regulated protein kinase (ERK) pathway activation (Ma et al., 2017). An increase of BDNF in serum of humans is associated with antidepressant therapy and clinical changes (Brunoni et al., 2008). Accordingly, BNDF serum levels might be a biomarker for the successful treatment of depression (Polyakova et al., 2015).

Little is known about the potential mediators of the BDNF induced antidepressant effects. Activation of TrkB by BDNF can enable three intracellular signaling pathways: i) phospholipase Cγ and subsequent IP_3, Ca^{2+} and protein kinase C activation ii) mitogen-activated protein kinase (MAPK) acting through the ERK pathway iii) phosphatidylinositol-3-kinase (PI3K) that can activate the AKT-mammalian target of rapamycin (mTOR) pathway (Park and Poo, 2013). The antidepressant effects of BDNF might be mediated by signaling through the ERK pathway (Lepack et al., 2016; Shirayama et al., 2002; Ma et al., 2017), since BDNF-TrkB signaling involves in many cases ERKs MAPK phosphorylation (Chao, 2003; Reichardt, 2006; Ma et al., 2017), but the AKT-mTOR pathway also appears to be involved (Duman, 2014; Lepack et al., 2016). Thus, the intracellular signaling pathways necessary for BDNF's antidepressant effects are still a matter of debate.

3. The function of p11 in depression and its regulation by antidepressants

P11 (also known as S100A10) is a member of the S100 gene family that acts as an adaptor protein and is critically involved in amplification of serotonergic signaling and the regulation of gene transcription (Svenningsson et al., 2013). P11 is downregulated in depressed humans and in a mouse model of depression and increased by electroconvulsive therapy or chronic administration of antidepressants including SSRIs. P11 mediates the antidepressant effects of BDNF and ketamine (Park et al., 2016; Sun et al., 2016; Warner-Schmidt et al., 2010). The induction of p11 by BDNF is mediated by signaling through the ERK pathway (Warner-Schmidt et al., 2010), in agreement with reports of an important role of this pathway in the mechanism of action of BDNF (Shirayama et al., 2002; Ma et al., 2017).

P11 appears to evoke its antidepressant effects in at least two ways (Svenningsson et al., 2013): It binds to the third intracellular loop of certain 5HT receptors ($5\text{-}HT_{1B}R$ and $5\text{-}HT_4R$) thereby increasing their cell surface expression and intracellular signaling such as calcium influx and ERKs activation. On the other hand, chronic treatment with SSRIs appears to upregulate p11 which facilitates the formation of a heterotetrameric complex of p11 with annexin A2, a member of the annexin family of proteins that regulate e.g. exocytosis, endocytosis, mitotic signaling and cytoskeleton rearrangements. The p11-annexin A2 complex binds to a chromatin-remodeling factor named SMARCA3 to form an even larger complex that is then targeted to the nuclear matrix, where it may have a role in regulating p11-dependent neurogenic effects (Svenningsson et al., 2013). The genes activated by the p11–annexin A2 – SMARCA3 chromatin remodeling complex are probably also involved in mediating the antidepressants effects of p11 (Oh et al., 2013).

However, an alternative mechanism for the antidepressant effects of p11 was identified recently (Lee et al., 2015). Thus, the p11-annexin A2 complex also binds to the cytoplasmic tail of the metabotropic glutamate receptor 5 (mGluR5) and increases its surface availability and signaling function. P11 and mGluR5 mutually facilitate their accumulation at the plasma membrane. Knockout of mGluR5 or p11 specifically in glutamatergic neurons in mice causes depression-like behavior, while knockout of mGluR5 or p11 in GABAergic interneurons causes antidepressant-like behavior. Thus, pro-depressant and anti-depressant effects of altered expression of p11 and mGluR5 depend on the relative extent of change of both proteins in glutamatergic and GABAergic neurons respectively. Accordingly, treatment with an mGluR5 non-competitive antagonist, 2-methyl-6-(phenylethynyl)pyridine (MPEP) induced antidepressant-like behaviors in a p11-dependent manner (Lee et al., 2015), since inhibition of mGluR5 function by MPEP in glutamatergic neurons is overcome by the MPEP-induced decrease of inhibitory input from GABAergic neurons.

4. The role of Homer1a as a universal mediator of pharmacological and non-pharmacological treatments of depression

The long homer scaffolding proteins such as Homer1 are proteins in the postsynaptic density (PSD) bridging metabotropic glutamate receptors such as mGluR1 and mGluR5 with many proteins involved in Ca^{2+} signaling, which have been implicated in the pathophysiology of mood disorders. The long Homer forms contain at their carboxy-terminal a coiled-coil (CC) structure followed by leucine zipper motifs that mediate Homer–Homer oligomerization and facilitate glutamate-mediated excitatory signaling (Szumlinski et al., 2006). They also form a polymeric network structure with other postsynaptic density proteins such as Shank (Hayashi et al., 2009). Thus, Homer proteins form a physical tether linking signaling molecules in postsynaptic densities. The short Homer1a is an immediate early gene (IEG) lacking the carboxyl-terminal domain and is considered as a dominant-negative