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Review

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Signaling pathways regulating Homer1a expression: implications for antidepressant therapy

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Abstract: Homer1a is upregulated by several different antidepressant measures, including non-pharmacological treatments, like sleep deprivation (SD) and electroconvulsive therapy (ECT) and antidepressant drugs, such as imipramine, fluoxetine and ketamine. Homer1a induction might thus be a crucial joint mechanism for antidepressant therapy in general. However, the upstream signaling pathways that regulate or induce Homer1a expression are still not well understood. The main focus of the present review is to offer an overview of the current knowledge about the potential role of Homer1a in depression and the signaling pathways responsible for Homer1a regulation. It is suggested here that a detailed characterization of the signaling mechanisms leading to Homer1a expression might provide novel therapeutic targets for antidepressant drug development.

Keywords: adenosine A_1 receptor; BDNF; depression; ERK pathway; Homer1a; Ras.

Introduction

Major depressive disorder is one of the most prevalent forms of mental illness. It is a complex and heterogeneous disorder, which imposes a severe economic burden on society (Krishnan and Nestler 2010). Most of the available antidepressant drugs require weeks or months to relieve the symptoms, they have low response and remittance rates and cause various side effects. The limited efficacy of the current antidepressants underlines the need to look for novel fast-acting and effective antidepressant measures. Treatment with a low dose of ketamine and non-pharmacological interventions, such as sleep deprivation (SD) and electroconvulsive therapy (ECT) emerged as rapid and effective antidepressant therapies, though their mechanism of action is not well understood (Berman et al., 2000; Kato, 2009; Benedetti and Colombo, 2011). A solid knowledge of the mechanism of action and the neurobiological effects of the current antidepressant therapies would facilitate the development of new antidepressant drugs.

Recently, we proposed that the induction of Homer1a, a neuronal immediate-early gene involved in the regulation of synaptic plasticity, is a common mechanism of action of several antidepressant treatments (Serchov et al., 2015a). The main focus of the present review is to offer an overview of the current knowledge about the relationship that Homer1a has with depression and with antidepressant therapy and the signaling pathways responsible for Homer1a regulation.

Homer1 proteins

The Homer family consists of three independent mammalian genes (Brakeman et al., 1997; Kato et al., 1998), each with several splice variants including the long isoform Homer1b/c and the short isoform Homer1a, which are the most studied among them (Bottai et al., 2002; Klugmann et al., 2005). The long Homer isoforms are constitutively expressed, while the expression of Homer1a is relatively low under normal conditions and similar to other immediate early genes (IEG) increases rapidly to neuronal

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activity (Brakeman et al., 1997). In contrast to BDNF, another complex IEG, which uses different promoters to switch from constitutive to activity-dependent expression (Timmusk et al., 1993), a different mechanism operates for Homer1. Homer1b/c and Homer1a are derived by alternative splicing of a common primary transcript adapting a constitutively expressed gene to function also as IEG. Homer1 gene contains promoter-distal and promoter-proximal functional poly(A) sites at the end of the exons corresponding, respectively to Homer1b/c and Homer1a (Bottai et al., 2002). Homer1a results from switching of the transcriptional termination from promoter-distal to promoter-proximal poly(A) site within the central intron 5. This process is enhanced by extracellular stimuli and it is independent from Homer1 promoter (Niibori et al., 2006). Unlike most IEGs that encode transcription factors, Homer1a is unique, because it functions directly at the synapses.

All Homer isoforms are characterized by a conserved N-terminal EVH1 ligand-binding domain, that interacts with many components of the postsynaptic density (PSD) (Brakeman et al., 1997; Kato et al., 1998; Xiao et al., 1998; Tu et al., 1998, 1999; Beneken et al., 2000; Feng et al., 2002; Hwang et al., 2003; Yuan et al., 2003). In addition to EVH1 domain, all long Homer isoforms, including Homer1b/c, exhibit a C-terminal coiled-coil (CC) domain, which mediates self-association and multimerization. Thus, via CC domain the constitutively expressed long Homer proteins act as scaffolding molecules that form a polymeric network structure at the PSD and facilitate clustering of specific synaptic proteins, modulating their activities at neuronal synapses (Xiao et al., 1998; Tu et al., 1988, 1999; Xiao et al., 2000; Hayashi et al., 2006, 2009). In addition to its role as an adaptor protein, it has been shown that Homer functions as ligand and directly modulates the Ca^{2+} release gain via ryanodine receptor (Feng et al., 2002). The long Homer1b/c links metabotropic glutamate receptors (mGluR1 and mGluR5) with NMDA receptors (Perroy et al., 2008; Bertaso et al., 2010) and many proteins involved in Ca^{2+} signaling (Tu et al., 1998; Feng et al., 2002; Hwang et al., 2003; Yuan et al., 2003), all of which have been implicated in the pathophysiology of mood disorders (Galeotti et al., 2008a,b; Krystal et al., 2010; Miller et al., 2014; Newell and Matosin, 2014). Therefore, abnormal clustering and declustering of Homer1b/c may provide an important mechanism that underlies the pathophysiological processes of depression (Szumlinski et al., 2006; Luo et al., 2012).

The short Homer1a lacks the CC domain and therefore does not form dimers with other Homer proteins (Brakeman et al., 1997; Kato et al., 1998). Instead it interferes with the scaffolding capability of long Homers by competitively binding the target proteins of Homer1b/c (Kammermeier and Worley, 2007). In general, Homer1a appears to be an important regulator of the activity-induced remodeling of synaptic structures (Inoue et al., 2007). Indeed, it has been identified as a member of the so-called plasticity-related proteins that promote persistent late phase synaptic plasticity (Okada et al., 2009). Thus, Homer1a provides flexible adaptation to environmental demands and as much as clinical depression can be seen as a result of failed adaptation to stress, Homer1a up-regulation might evoke its antidepressant effects by improving synaptic reorganization in neural networks salient for mood regulation.

Homer1a in depression and antidepressant treatments

The potential involvement of Homer1a in depression-like behavior has been suggested in several reports (Lominac et al., 2005; Szumlinski et al., 2005, 2006; Kato, 2009; Rietschel et al., 2010; Sun et al., 2011). Collectively, the data on Homer1 suggest distinct roles for both isoforms: Homer1a and Homer1b/c in behavioral response to stress. General deletion of Homer1 enhances anxiety- and depression-like behavior in mice (Szumlinski et al., 2005). Homer1 knockout (KO) mice have elevated plasma levels of corticosterone and aldosterone (Grinevich et al., 2011), suggesting that Homer1 is involved in the regulation of hypothalamic-pituitary-adrenal axis activity (Grinevich et al., 2012). The amplified behavioral response to stressors in Homer1KO mice appears to result from an inability to induce an increase of Homer1a in the medial prefrontal cortex (mPFC), because adeno-associated virus-mediated restoration of Homer1a in the mPFC of KO mice relieves the depression-like behavior (Lominac et al., 2005). In contrast, restoration of Homer1b/c in mPFC of Homer1KO mice even enhance genotypic differences (Lominac et al., 2005), consistent with anxiogenic effects observed by hippocampal overexpression of Homer1g, a Homer1 isoform possessing only CC domain (Klugmann et al., 2005). Thus, an induction of Homer1a within cortical structures facilitates the ability to cope with stressors, whereas the overexpression of the CC-Homer1 isoforms leads to behavioral debilitation (Szumlinski et al., 2006). In support of this proposition, we demonstrated that mice subjected to model of chronic depression (CDM) show reduced Homer1a expression in the mPFC, whereas treatment with several antidepressant measures, including chronic treatment with classical

antidepressants, like imipramine and fluoxetine, as well as acute ketamine treatment or 6 h of SD strongly increase Homer1a levels in this region (Serchov et al., 2015a). Interestingly, specific siRNA knockdown of Homer1a in mPFC enhances depressive-like behavior and prevented the antidepressant effects of SD, imipramine and ketamine treatment, while viral overexpression of Homer1a in this region promotes antidepressant effects, demonstrating that Homer1a expression specifically in the mPFC is inversely correlated to the depressive-like behavior (Serchov et al., 2015a). In addition, non-pharmacological treatments of depression, like ECT and transcranial magnetic stimulation, a less invasive non-pharmacological antidepressant treatment, alternative to ECT, also upregulate Homer1a expression levels in the cortex (Sakagami et al., 2005; Conti et al., 2007; Sun et al., 2011). Indeed, Homer1a was proposed to be instrumental for the therapeutic effect of ECT in depression (Sakagami et al., 2005; Kato, 2009). Therefore, we proposed that the induction of Homer1a is a final common pathway mediating the antidepressant effects of different antidepressant treatments (Figure 1) (Serchov et al., 2015a). Taken together these data point towards a general importance of Homer1a for antidepressant therapy. However, the upstream signaling pathways that regulate or induce Homer1a expression are still not well investigated.

Adenosine A_1 receptor (A_1R) signaling to Homer1a in antidepressant therapy

Several non-pharmacological treatments of depression are associated with increased adenosinergic signaling

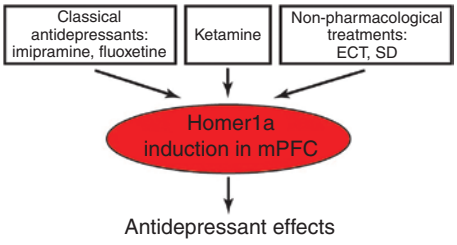

Figure 1: Homer1a induction mediates the antidepressant effects of several antidepressant treatments.
The antidepressant effects of the chronic treatment with classical antidepressants, such as imipramine or fluoxetine, non-pharmacological treatments, like SD and ECT, as well as single dose of ketamine are all accompanied and strictly dependent on the increased expression of Homer1a in the mPFC.

(van Calker and Biber, 2005; Burnstock et al., 2011; Sadek et al., 2011). Adenosine is a neuromodulator in the central nervous system exhibiting anticonvulsive, neuroprotective and sleep regulating properties (Fredholm et al., 2005). Adenosine's actions are mediated by four receptor subtypes, A_1, A_{2A}, A_{2B} and A_3 (Fredholm et al., 2001). It is known that SD evokes an increased release of adenosine in the brain and up-regulation of adenosine A_1 receptors (A_1R) in rodents and humans (Basheer et al., 2007; Elmenhorst et al., 2007, 2009). Two other non-pharmacological interventions for depression ECT and deep brain stimulation are associated with an increased release of adenosine and stimulation of A_1R (van Calker and Biber, 2005; Bekar et al., 2008; Hamani et al., 2010; Sadek et al., 2011). Furthermore, direct experimental data indicate that adenosine agonists have antidepressant activity (Hines et al., 2013). Recently, we demonstrated that conditional doxycycline-regulated upregulation of A_1R expression (Serchov et al., 2012) in the forebrain neurons of transgenic mice (A1 mice) leads to pronounced acute and chronic resilience towards depressive-like behavior in various tests (Serchov et al., 2015a). Conversely, A_1RKO mice displayed an increased depressive-like behavior and were resistant to the antidepressant effects of SD (Serchov et al., 2015a).

Interestingly, Homer1a is up-regulated by SD and ECT, antidepressant therapies also associated with increased A_1R signaling (Sakagami et al., 2005; Conti et al., 2007; Elmenhorst et al., 2007, 2009; Sadek et al., 2011). We described that Homer1a expression is increased in the brain of A1 mice, while A_1RKO mice have low Homer1a levels and display no induction of Homer1a in mPFC after SD (Serchov et al., 2015a). In addition, agonist stimulation of A_1R *in vitro* in primary neuronal cultures and *in vivo* in mice increases Homer1a expression (Serchov et al., 2015a). A_1R are usually coupled with Gi proteins, that inhibit cAMP formation (Fredholm et al., 2001), but when highly expressed in cells (e.g. neurons or smooth muscle cells) A_1R can also regulate phospholipase C (PLC) (Biber et al., 1997; Rogel et al., 2006; Fenton et al., 2010; Robin et al., 2011) and extracellular signal-regulated kinase (ERK) pathway (Migita et al., 2008; Kunduri et al., 2013). Indeed, inhibition of PLC or ERK1,2 completely abolishes the A_1R mediated increase of Homer1a expression in primary neurons (Serchov et al., 2015a). In addition, *in vivo* application of the A_1R agonist MRS5474 induces ERK1,2 activation and Homer1a levels in the mouse cortex (Serchov et al., 2015a), corroborating previous reports on ERKs in Homer1a regulation (Sato et al. 2001; Mahan et al., 2012; Wang et al., 2012) and providing evidence for the importance of this signaling route in depression. Taken together these reports suggest that several non-pharmacological

treatments of depression elicit their antidepressant effects by activation of A_1R-ERK1,2 signaling mediated induction of Homer1a (Figure 2).

BDNF/Ras/ERK-mediated regulation of Homer1a in depression

Several lines of evidence show that chronic treatment with classical antidepressants, like imipramine and fluoxetine upregulate Homer1a expression (Conti et al., 2007; Sun et al., 2011; Serchov et al., 2015a). The fact that these drugs require at least 2 weeks to increase Homer1a suggests for indirect mechanism of regulation (Serchov et al., 2015a). Such a mechanism might be explained by the neurotrophin hypothesis, which is one of the leading hypothesis towards the neurobiological basis of depression and which focuses on the role of brain-derived neurotrophic factor (BDNF). Chronic stress, a major risk factor for development of depressive episodes, and a subsequent rise in plasma corticosteroid levels, causes a decrease in BDNF levels in several brain regions implicated in the physiology of depression (Smith et al., 1995). Conversely, a stress-induced downregulation of BDNF can be reversed by antidepressants or ECT, consistent with a delayed onset of the clinical efficacy of these treatments (Nibuya et al., 1995). Moreover, intraventricular BDNF infusion causes rapid and sustained antidepressant-like effects (Shirayama et al., 2002). In addition, the antidepressant effects of ketamine require BDNF as ketamine is not affecting BDNF-deficient mice (Autry et al., 2011).

According to the neurotrophin hypothesis, chronic treatment with classical antidepressants activate the transcriptional factor cAMP response element binding protein (CREB), which enhances BDNF expression (Figure 2) (Nibuya et al., 1996; Thome et al., 2000). One of the best studied BDNF-regulated signaling cascades is the ERK pathway (Heumann, 1994). The activation of ERK-pathway is mediated by Ras-induced MEK1,2 activation, that phosphorylates ERK1,2 (Figure 2) (Katz and McCormick, 1997). Several studies have suggested that the BDNF-Ras-ERK pathway is implicated in the control of depressive-like behavior. The acute blockade of the ERK-pathway by MEK1,2 inhibition produces depressive-like phenotype and inhibits the effects of BDNF and several antidepressant drugs on behavior (Shirayama et al., 2002; Duman et al., 2007). The BDNF-Ras-ERK pathway in turn couples

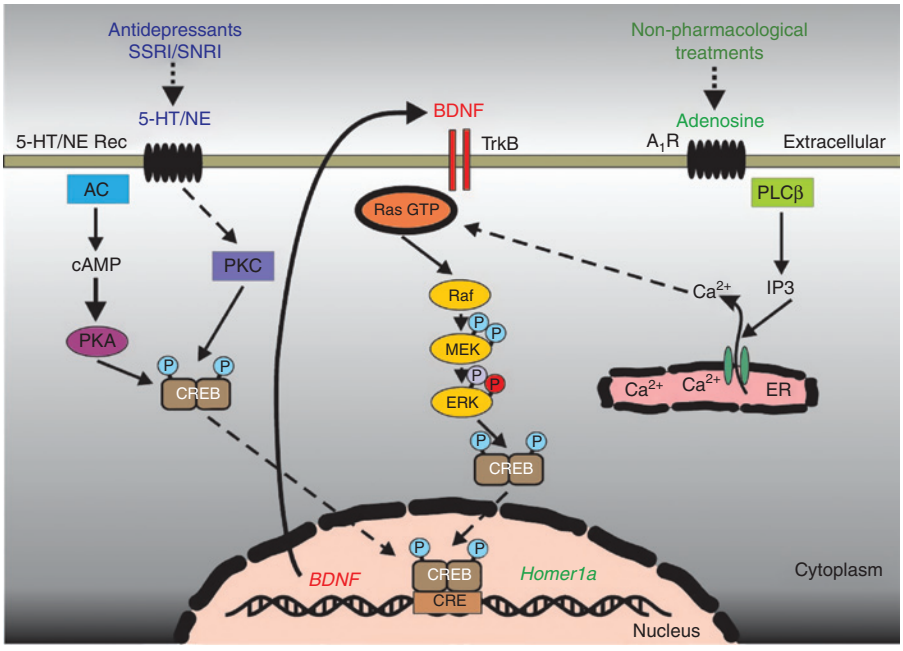

Figure 2: Signaling pathways regulating Homer1a expression.
According to the neurotrophin hypothesis, classical antidepressant medications, like selective serotonin reuptake inhibitors (SSRI) and selective noradrenaline reuptake inhibitors (SNRI), activate by an increase of serotonin (5HT) and noradrenaline (NE) mediated signaling the transcription factor CREB, which enhances BDNF expression. BDNF, in turn, induces Homer1a expression via TrkB receptor-Ras-ERK-CREB signaling cascade. Furthermore, several non-pharmacological treatments of depression, like SD, ECT and deep brain stimulation, lead to increased A_1R signaling. In turn, activated adenosine A_1 receptor (A_1R) upregulates Homer1a levels by PLCβ-IP3-Ca^{2+}-mediated activation of the ERK pathway; endoplasmic reticulum (ER).

to CREB phosphorylation (Figure 2) (Xing et al., 1996). At the clinical level, postmortem investigations have shown that untreated depressive patients have lower levels of CREB and phosphorylated CREB in the cortex compared to healthy controls. In contrast, higher concentration of CREB was detected in patients under antidepressant medication compared to untreated patients (Dowlatshani et al., 1998; Yamada et al., 2003). Taken together these results indicate that stress and depression coincide with a decreased activity of the BDNF-Ras-ERK-CREB pathway, while antidepressants evoke an activation of this signaling cascade.

Several reports demonstrate that the BDNF-ERK pathway plays an important role in the activity-dependent regulation of Homer1a (Sato et al. 2001; Mahan et al., 2012; Wang et al., 2012). *In vitro* study in primary neuronal cultures showed that BDNF, selectively via ERK1,2 activation, upregulates Homer1a mRNA and protein levels (Sato et al., 2001). Furthermore, Mahan et al. (2012) reported that BDNF increases Homer1a mRNA expression in an ERK-dependent manner via epigenetic modulation of Homer1a transcription. BDNF stimulation strongly increases histone H3 acetylation or decreases H3K9 methylation around the Homer1 promoter, resulting in enhanced Homer1a expression (Mahan et al., 2012). Interestingly, the promoter region of the Homer1 gene family contains several CRE binding sites, suggesting CREB mediation of gene transcription (Mahan et al., 2012). These data suggest that the antidepressant drugs induced upregulation of Homer1a might be mediated by the BDNF-Ras-ERK-CREB pathway (Figure 2).

A recent report showed that chronic photic stimulation in mice has antidepressant effects and increases Homer1a expression in the cortex (Sun et al., 2015). Interestingly, we have demonstrated light-induced regulation of the Ras signaling cascade (Serchov and Heumann, 2006; Serchov et al., 2015b). In order to study the role of Ras, we have generated a transgenic mouse model expressing constitutively activated Ras selectively in neurons (synRas mice) (Heumann et al., 2000). As Ras appears to be the major effector of BDNF signaling and one of the main upstream regulators of the ERK pathway resulting in elevated levels of CREB phosphorylation (Hansen et al., 2004), such a mouse model might be a suitable approach to study the role of upstream signaling pathways regulating Homer1a in depression.

Conclusions and future prospectives

As the antidepressant effects mediated by chronic treatment with classical antidepressant medications, like imipramine and fluoxetine, as well as the very rapid actions of ketamine and SD are all accompanied by and strictly dependent on an increased expression of Homer1a specifically in the mPFC, it is concluded that Homer1a induction is a crucial joint mechanism mediating the antidepressant effects. However, how Homer1a mediates antidepressant effects is currently unknown. As the key scaffolding molecule at the PSD, constitutively expressed long Homers form a polymeric network complexes linking mGluR5 with NMDA receptors and various proteins involved in Ca^{2+} homeostasis (Tu et al., 1998; Feng et al., 2002; Hwang et al., 2003; Yuan et al., 2003; Perroy et al., 2008; Bertaso et al., 2010), which have been all implicated in the pathophysiology and treatment of depression (Galeotti et al., 2008a,b; Krystal et al., 2010; Miller et al., 2014; Newell and Matosin, 2014). The induction of Homer1a, which acts as a dominant negative protein and declusters long Homer complexes, might serve as a therapeutic method in depression to modulate activity of the target proteins. Interestingly, several studies have shown that *in vivo* and *in vitro* application of a decoy peptide, which contains the Homer binding site of mGluR5, specifically disrupts mGluR5/Homer interactions and mimics the effects of Homer1a induction (Yang et al., 2004; Mao et al., 2005; Ronesi and Huber, 2008; Tronson et al., 2010). Further investigation of the effects of this peptide in depression might provide insights on the mechanism of action of Homer1a and might be adopted as a novel approach to treat depression.

The reports presented here indicate the ERK signaling cascade to be a key mediator that links distinct antidepressant treatments to the transcriptional induction of Homer1a. On the one hand, various non-pharmacological treatments, which are associated with increased A_1R signaling, might result in ERK1,2 stimulation via PLC activation, subsequent production of IP_3 and intracellular Ca^{2+} release. On the other hand, several antidepressant drugs, both classical and novel, increase BDNF expression and activate the BDNF-Ras-ERK pathway. However, besides the ERK-dependent epigenetic modulation of Homer1a transcription, the precise mechanism of ERK-mediated regulation of Homer1a is not clear. Thus, further characterization of the signaling mechanisms stimulating Homer1a expression might provide novel therapeutic targets for antidepressant drug development.

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