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Review

Tsvetan Serchov*, Rolf Heumann, Dietrich van Calker and Knut Biber

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 A₁ 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 A₁ receptor (A₁R) 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, A₁, A_{2A}, A_{2B} and A₃ (Fredholm et al., 2001). It is known that SD evokes an increased release of adenosine in the brain and up-regulation of adenosine A₁ receptors (A₁R) 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 A₁R (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 A₁R 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, A₁RKO 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 A₁R 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 A₁RKO mice have low Homer1a levels and display no induction of Homer1a in mPFC after SD (Serchov et al., 2015a). In addition, agonist stimulation of A₁R *in vitro* in primary neuronal cultures and *in vivo* in mice increases Homer1a expression (Serchov et al., 2015a). A₁R 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) A₁R 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 A₁R mediated increase of Homer1a expression in primary neurons (Serchov et al., 2015a). In addition, *in vivo* application of the A₁R 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 A₁R-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 A₁R signaling. In turn, activated adenosine A₁ receptor (A₁R) upregulates Homer1a levels by PLCβ-IP3-Ca²⁺-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 (Dowlatschani 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 perspectives

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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References

- Autry, A.E., Adachi, M., Nosyreva, E., Na, E.S., Los, M.F., Cheng, P.F., Kavalali, E.T., and Monteggia, L.M. (2011). NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature* 475, 91–95.
- Basheer, R., Bauer, A., Elmenhorst, D., Ramesh, V., and McCarley, R.W. (2007). Sleep deprivation upregulates A1 adenosine receptors in the rat basal forebrain. *Neuroreport* 18, 1895–1899.
- Bekar, L., Libionka, W., Tian, G.F., Xu, Q., Torres, A., Wang, X., Lovatt, D., Williams, E., Takano, T., Schnermann, J., et al. (2008). Adenosine is crucial for deep brain stimulation-mediated attenuation of tremor. *Nat. Med.* 14, 75–80.
- Benedetti, F. and Colombo, C. (2011). Sleep deprivation in mood disorders. *Neuropsychobiology* 64, 141–151.
- Beneken, J., Tu, J.C., Xiao, B., Nuriya, M., Yuan, J.P., Worley, P.F., and Leahy, D.J. (2000). Structure of the Homer EVH1 domain-peptide complex reveals a new twist in polyproline recognition. *Neuron* 26, 143–154.
- Berman, R.M., Cappiello, A., Anand, A., Oren, D.A., Heninger, G.R., Charney, D.S., and Krystal, J.H. (2000). Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry* 47, 351–354.
- Bertaso, F., Roussignol, G., Worley, P., Bockaert, J., Fagni, L., and Ango, F. (2010). Homer1a-dependent crosstalk between NMDA and metabotropic glutamate receptors in mouse neurons. *PLoS One* 5, e9755.
- Biber, K., Klotz, K.N., Berger, M., Gebicke-Harter, P.J., and van Calker, D. (1997). Adenosine A1 receptor-mediated activation of phospholipase C in cultured astrocytes depends on the level of receptor expression. *J. Neurosci.* 17, 4956–4964.
- Bottai, D., Guzowski, J.F., Schwarz, M.K., Kang, S.H., Xiao, B., Lanahan, A., Worley, P.F., and Seeburg, P.H. (2002). Synaptic activity-induced conversion of intronic to exonic sequence in Homer 1 immediate early gene expression. *J. Neurosci.* 22, 167–175.
- Brakeman, P.R., Lanahan, A.A., O'Brien, R., Roche, K., Barnes, C.A., Huganir, R.L., and Worley, P.F. (1997). Homer: a protein that selectively binds metabotropic glutamate receptors. *Nature* 386, 284–288.
- Burnstock, G., Krugel, U., Abbracchio, M.P., and Illes, P. (2011). Purinergic signalling: from normal behaviour to pathological brain function. *Prog. Neurobiol.* 95, 229–274.
- Conti, B., Maier, R., Barr, A.M., Morale, M.C., Lu, X., Sanna, P.P., Bilbe, G., Hoyer, D., and Bartfai, T. (2007). Region-specific transcriptional changes following the three antidepressant treatments electro convulsive therapy, sleep deprivation and fluoxetine. *Mol. Psychiatry* 12, 167–189.
- Dowlatsani, D., MacQueen, G.M., Wang, J.F., and Young, L.T. (1998). Increased temporal cortex CREB concentration and antidepressant treatment in major depression. *Br. J. Psychiatry* 174, 429–433.
- Duman, C.H., Schlesinger, L., Kodama, M., Russel, D.S., and Duman, R.S. (2007). A role for MAP kinase signaling in behavioral models of depression and antidepressant treatment. *Biol. Psychiatry* 61, 661–670.
- Elmenhorst, D., Meyer, P.T., Winz, O.H., Matusch, A., Ermer, J., Coenen, H.H., Basheer, R., Haas, H.L., Zilles, K., and Bauer, A. (2007). Sleep deprivation increases A1 adenosine receptor binding in the human brain: a positron emission tomography study. *J. Neurosci.* 27, 2410–2415.
- Elmenhorst, D., Basheer, R., McCarley, R.W., and Bauer, A. (2009). Sleep deprivation increases A(1) adenosine receptor density in the rat brain. *Brain Res.* 1258, 53–58.
- Feng, W., Tu, J., Yang, T., Vernon, P.S., Allen, P.D., Worley, P.F., and Pessah, I.N. (2002). Homer regulates gain of ryanodine receptor type 1 channel complex. *J. Biol. Chem.* 277, 44722–44730.
- Fenton, R.A., Shea, L.G., Doddi, C., and Dobson, J.G., Jr. (2010). Myocardial adenosine A(1)-receptor-mediated adenosine protection involves phospholipase C, PKC-epsilon, and p38 MAPK, but not HSP27. *Am. J. Physiol. Heart Circ. Physiol.* 298, H1671–H1678.
- Fredholm, B.B., IJerman, A.P., Jacobson, K.A., Klotz, K.N., and Linden, J. (2001). International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. *Pharmacol. Rev.* 53, 527–552.
- Fredholm, B.B., Chen, J.F., Cunha, R.A., Svenningsson, P., and Vaugeois, J.M. (2005). Adenosine and brain function. *Int. Rev. Neurobiol.* 63, 191–270.
- Galeotti, N., Vivoli, E., Bartolini, A., and Ghelardini, C. (2008a). A gene-specific cerebral types 1, 2, and 3 RyR protein knockdown induces an antidepressant-like effect in mice. *J. Neurochem.* 106, 2385–2394.
- Galeotti, N., Vivoli, E., Norcini, M., Bartolini, A., and Ghelardini, C. (2008b). An antidepressant behaviour in mice carrying a gene-specific InsP3R1, InsP3R2 and InsP3R3 protein knockdown. *Neuropharmacology* 55, 1156–1164.
- Grinevich, V., Jezova, D., Gambaryan, S., Illarionova, A., Kolleker, A., Seeburg, P.H., and Schwarz, M.K. (2011). Hypertrophy and altered activity of the adrenal cortex in Homer 1 knockout mice. *Horm. Metab. Res.* 43, 551–556.
- Grinevich, V., Seeburg, P.H., Schwarz, M.K., and Jezova, D. (2012). Homer 1-a new player linking the hypothalamic-pituitary-adrenal axis activity to depression and anxiety. *Endocr. Regul.* 46, 153–159.
- Hamani, C., Diwan, M., Macedo, C.E., Brandao, M.L., Shumake, J., Gonzalez-Lima, F., Raymond, R., Lozano, A.M., Fletcher, P.J., and Nobrega, J.N. (2010). Antidepressant-like effects of medial prefrontal cortex deep brain stimulation in rats. *Biol. Psychiatry* 67, 117–124.
- Hansen, H.H., Briem, T., Dzietko, M., Siffringer, M., Voss, A., Rzeski, W., Zdzisinska, B., Thor, F., Heumann, R., Stepulak, A., et al. (2004). Mechanisms leading to disseminated apoptosis following NMDA receptor blockade in the developing rat brain. *Neurobiol. Dis.* 16, 440–453.
- Hayashi, M.K., Ames, H.M., and Hayashi, Y. (2006). Tetrameric hub structure of postsynaptic scaffolding protein homer. *J. Neurosci.* 26, 8492–8501.
- Hayashi, M.K., Tang, C., Verpelli, C., Narayanan, R., Stearns, M.H., Xu, R.M., Li, H., Sala, C., and Hayashi, Y. (2009). The postsynaptic density proteins Homer and Shank form a polymeric network structure. *Cell* 137, 159–171.
- Heumann, R. (1994). Neurotrophin signalling. *Curr. Opin. Neurobiol.* 4, 668–679.
- Heumann, R., Goemans, C., Bartsch, D., Lingenhöhl, K., Waldmeier, P.C., Hengerer, B., Allegrini, P.R., Schellander, K., Wagner, E.F., Arendt, T., et al. (2000). Transgenic activation of Ras in neurons promotes hypertrophy and protects from lesion-induced degeneration. *J. Cell. Biol.* 151, 1537–1548.

- Hines, D.J., Schmitt, L.I., Hines, R.M., Moss, S.J., and Haydon, P.G. (2013). Antidepressant effects of sleep deprivation require astrocyte-dependent adenosine mediated signaling. *Transl. Psychiatry* 3, e212.
- Hwang, S.Y., Wei, J., Westhoff, J.H., Duncan, R.S., Ozawa, F., Volpe, P., Inokuchi, K., and Koulen, P. (2003). Differential functional interaction of two Vesl/Homer protein isoforms with ryanodine receptor type 1: a novel mechanism for control of intracellular calcium signaling. *Cell. Calcium* 34, 177–184.
- Inoue, Y., Udo, H., Inokuchi, K., and Sugiyama, H. (2007). Homer1a regulates the activity-induced remodeling of synaptic structures in cultured hippocampal neurons. *Neuroscience* 150, 841–852.
- Kammermeier, P.J. and Worley, P.F. (2007). Homer 1a uncouples metabotropic glutamate receptor 5 from postsynaptic effectors. *Proc. Natl. Acad. Sci. USA* 104, 6055–6060.
- Kato, N. (2009). Neurophysiological mechanisms of electroconvulsive therapy for depression. *Neurosci. Res.* 64, 3–11.
- Kato, A., Ozawa, F., Saitoh, Y., Fukazawa, Y., Sugiyama, H., and Inokuchi, K. (1998). Novel members of the Vesl/Homer family of PDZ proteins that bind metabotropic glutamate receptors. *J. Biol. Chem.* 273, 23969–23975.
- Katz, M.E. and McCormick, F. (1997). Signal transduction from multiple Ras effectors. *Curr. Opin. Genet. Dev.* 7, 75–79.
- Klugmann, M., Symes, C.W., Leichtlein, C.B., Klausner, B.K., Dunning, J., Fong, D., Young, D., and During, M.J. (2005). AAV-mediated hippocampal expression of short and long Homer 1 proteins differentially affect cognition and seizure activity in adult rats. *Mol. Cell. Neurosci.* 28, 347–360.
- Krishnan, V. and Nestler, E.J. (2010). Linking molecules to mood: new insight into the biology of depression. *Am. J. Psychiatry* 167, 1305–1320.
- Krystal, J.H., Mathew, S.J., D'Souza, D.C., Garakani, A., Gunduz-Bruce, H., and Charney, D.S. (2010). Potential psychiatric applications of metabotropic glutamate receptor agonists and antagonists. *CNS Drugs* 24, 669–693.
- Kunduri, S.S., Mustafa, S.J., Ponnoth, D.S., Dick, G.M., and Nayeem, M.A. (2013). Adenosine A1 receptors link to smooth muscle contraction via CYP4a, protein kinase C- α , and ERK1/2. *J. Cardiovasc. Pharmacol.* 62, 78–83.
- Lominac, K.D., Oleson, E.B., Pava, M., Klugmann, M., Schwarz, M.K., Seeburg, P.H., During, M.J., Worley, P.F., Kalivas, P.W., and Szumlanski, K.K. (2005). Distinct roles for different Homer1 isoforms in behaviors and associated prefrontal cortex function. *J. Neurosci.* 25, 11586–11594.
- Luo, P., Li, X., Fei, Z., and Poon, W. (2012). Scaffold protein Homer 1: implications for neurological diseases. *Neurochem. Int.* 61, 731–738.
- Mahan, A.L., Mou, L., Shah, N., Hu, J.H., Worley, P.F., and Ressler, K.J. (2012). Epigenetic modulation of Homer1a transcription regulation in amygdala and hippocampus with pavlovian fear conditioning. *J. Neurosci.* 32, 4651–4659.
- Mao, L., Yang, L., Tang, Q., Samdani, S., Zhang, G., and Wang, J.Q. (2005). The scaffold protein Homer1b/c links metabotropic glutamate receptor 5 to extracellular signal-regulated protein kinase cascades in neurons. *J. Neurosci.* 25, 2741–2752.
- Migita, H., Kominami, K., Higashida, M., Maruyama, R., Tsuchida, N., McDonald, F., Shimada, F., and Sakurada, K. (2008). Activation of adenosine A1 receptor-induced neural stem cell proliferation via MEK/ERK and Akt signaling pathways. *J. Neurosci. Res.* 86, 2820–2828.
- Miller, O.H., Yang, L., Wang, C.C., Hargroder, E.A., Zhang, Y., Delpire, E., and Hall, B.J. (2014). GluN2B-containing NMDA receptors regulate depression-like behavior and are critical for the rapid antidepressant actions of ketamine. *eLife* 3, e03581.
- Newell, K.A. and Matosin, N. (2014). Rethinking metabotropic glutamate receptor 5 pathological findings in psychiatric disorders: implications for the future of novel therapeutics. *BMC Psychiatry* 14, 23.
- Nibuya, M., Morinobu, S., and Duman, R.S. (1995). Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J. Neurosci.* 15, 7539–7547.
- Nibuya, M., Nestler, E.J., and Duman, R.S. (1996). Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J. Neurosci.* 16, 2365–2372.
- Niibori, Y., Hayashi, F., Hirai, K., Matsui, M., and Inokuchi, K. (2006). Alternative poly(A) site-selection regulates the production of alternatively spliced vesl-1/homer1 isoforms that encode post-synaptic scaffolding proteins. *Neurosci. Res.* 57, 399–410.
- Okada, D., Ozawa, F., and Inokuchi, K. (2009). Input-specific spine entry of soma-derived Vesl-1S protein conforms to synaptic tagging. *Science* 324, 904–909.
- Perroy, J., Raynaud, F., Homburger, V., Rousset, M.C., Telley, L., Bockaert, J., and Fagni, L. (2008). Direct interaction enables cross-talk between ionotropic and group I metabotropic glutamate receptors. *J. Biol. Chem.* 283, 6799–6805.
- Rietschel, M., Mattheisen, M., Frank, J., Treutlein, J., Degenhardt, F., Breuer, R., Steffens, M., Mier, D., Esslinger, C., Walter, H., et al. (2010). Genome-wide association-, replication-, and neuroimaging study implicates HOMER1 in the etiology of major depression. *Biol. Psychiatry* 68, 578–585.
- Robin, E., Sabourin, J., Benoit, R., Pedretti, S., and Raddatz, E. (2011). Adenosine A1 receptor activation is arrhythmogenic in the developing heart through NADPH oxidase/ERK- and PLC/PKC-dependent mechanisms. *J. Mol. Cell. Cardiol.* 51, 945–954.
- Rogel, A., Bromberg, Y., Sperling, O., and Zoref-Shani, E. (2006). The neuroprotective adenosine-activated signal transduction pathway involves activation of phospholipase C. *Nucleosides Nucleotides Nucleic Acids* 25, 1283–1286.
- Ronesi, J.A. and Huber, K.M. (2008). Homer interactions are necessary for metabotropic glutamate receptor-induced long-term depression and translational activation. *J. Neurosci.* 28, 543–547.
- Sadek, A.R., Knight, G.E., and Burnstock, G. (2011). Electroconvulsive therapy: a novel hypothesis for the involvement of purinergic signalling. *Purinergic Signal.* 7, 447–452.
- Sakagami, Y., Yamamoto, K., Sugiura, S., Inokuchi, K., Hayashi, T., and Kato, N. (2005). Essential roles of Homer-1a in homeostatic regulation of pyramidal cell excitability: a possible link to clinical benefits of electroconvulsive shock. *Eur. J. Neurosci.* 21, 3229–3239.
- Sato, M., Suzuki, K., and Nakanishi, S. (2001). NMDA receptor stimulation and brain-derived neurotrophic factor upregulate homer 1a mRNA via the mitogen-activated protein kinase cascade in cultured cerebellar granule cells. *J. Neurosci.* 21, 3797–3805.
- Shirayama, Y., Chen, A.C., Nakagawa, S., Russel, D.S., and Duman, R.S. (2002). Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *J. Neurosci.* 22, 3251–3261.

- Serchov, T. and Heumann, R. (2006). Constitutive activation of ras in neurons: implications for the regulation of the mammalian circadian clock. *Chronobiol. Int.* 23, 191–200.
- Serchov, T., Atas, H.C., Normann, C., van Calker, D., and Biber, K. (2012). Genetically controlled upregulation of adenosine A(1) receptor expression enhances the survival of primary cortical neurons. *Mol. Neurobiol.* 46, 535–544.
- Serchov, T., Clement, H.W., Schwarz, M.K., Iasevoli, F., Tosh, D.K., Idzko, M., Jacobson, K.A., de Bartolomeis, A., Normann, C., Biber, K., et al. (2015a). Increased signaling via adenosine A1 receptors, sleep deprivation, imipramine, and ketamine inhibit depressive-like behavior via induction of Homer1a. *Neuron* 87, 549–562.
- Serchov, T., Jilg, A., Wolf, C.T., Radtke, I., Stehle, J.H., and Heumann, R. (2015b). Ras activity oscillates in the mouse suprachiasmatic nucleus and modulates circadian clock dynamics. *Mol. Neurobiol.* March 12 [Epub ahead of print], doi:10.1007/s12035-015-9135-0.
- Smith, M.A., Makino, S., Kvetnansky, R., and Post, R.M. (1995). Effects of stress on neurotrophic factor expression in the rat brain. *Ann. N.Y. Acad. Sci.* 771, 234–239.
- Sun, P., Wang, F., Wang, L., Zhang, Y., Yamamoto, R., Sugai, T., Zhang, Q., Wang, Z., and Kato, N. (2011). Increase in cortical pyramidal cell excitability accompanies depression-like behavior in mice: a transcranial magnetic stimulation study. *J. Neurosci.* 31, 16464–16472.
- Sun, P., Zhang, Q., Zhang, Y., Wang, F., Chen, R., Yamamoto, R., and Kato, N. (2015). Homer1a-dependent recovery from depression-like behavior by photic stimulation in mice. *Physiol. Behav.* 147, 334–341.
- Szumliński, K.K., Lominac, K.D., Kleschen, M.J., Oleson, E.B., Dehoff, M.H., Schwarz, M.K., Seeburg, P.H., Worley, P.F., and Kalivas, P.W. (2005). Behavioral and neurochemical phenotyping of Homer1 mutant mice: possible relevance to schizophrenia. *Gen. Brain Behav.* 4, 273–288.
- Szumliński, K.K., Kalivas, P.W., and Worley, P.F. (2006). Homer proteins: implications for neuropsychiatric disorders. *Curr. Opin. Neurobiol.* 16, 251–257.
- Thome, J., Sakai, N., Shin, K., Steffen, C., Zhang, Y.J., Impey, S., Storm, D., and Duman, R.S. (2000). cAMP response element-mediated gene transcription is upregulated by chronic antidepressant treatment. *J. Neurosci.* 20, 4030–4036.
- Timmusk, T., Palm, K., Metsis, M., Reintam, T., Paalme, V., Saarma, M., and Persson, H. (1993). Multiple promoters direct tissue-specific expression of the rat BDNF gene. *Neuron* 10, 475–489.
- Tronson, N.C., Guzman, Y.F., Guedea, A.L., Huh, K.H., Gao, C., Schwarz, M.K., and Radulovic, J. (2010). Metabotropic glutamate receptor 5/Homer interactions underlie stress effects on fear. *Biol. Psychiatry* 68, 1007–1015.
- Tu, J.C., Xiao, B., Yuan, J.P., Lanahan, A.A., Leoffert, K., Li, M., Linden, D.J., and Worley, P.F. (1998). Homer binds a novel proline-rich motif and links group 1 metabotropic glutamate receptors with IP3 receptors. *Neuron* 21, 717–726.
- Tu, J.C., Xiao, B., Naisbitt, S., Yuan, J.P., Petralia, R.S., Brakeman, P., Doan, A., Aakalu, V.K., Lanahan, A.A., Sheng, M., et al. (1999). Coupling of mGluR/Homer and PSD-95 complexes by the Shank family of postsynaptic density proteins. *Neuron* 23, 583–592.
- van Calker, D. and Biber, K. (2005). The role of glial adenosine receptors in neural resilience and the neurobiology of mood disorders. *Neurochem. Res.* 30, 1205–1217.
- Wang, Y., Fei, Z., Ma, Y.H., Liu, W.B., Zhu, J., Zhang, C., Lin, W., and Qu, Y. (2012). VEGF upregulates Homer 1a gene expression via the mitogen-activated protein kinase cascade in cultured cortex neurons. *Neurosci. Lett.* 515, 44–49.
- Xiao, B., Tu, J.C., Petralia, R.S., Yuan, J.P., Doan, A., Breder, C.D., Ruggiero, A., Lanahan, A.A., Wenthold, R.J., and Worley, P.F. (1998). Homer regulates the association of group 1 metabotropic glutamate receptors with multivalent complexes of homer-related, synaptic proteins. *Neuron* 21, 707–716.
- Xiao, B., Tu, J.C., and Worley, P.F. (2000). Homer: a link between neural activity and glutamate receptor function. *Curr. Opin. Neurobiol.* 10, 370–374.
- Xing, J., Ginty, D.D., and Greenberg, M.E. (1996). Coupling of the RAS-MAPK pathway to gene activation by RSK2, a growth factor-regulated CREB kinase. *Science* 273, 959–963.
- Yamada, S., Yamamoto, M., Ozawa, H., Riederer, P., and Saito, T. (2003). Reduced phosphorylation of cyclic AMP-responsive element binding protein in the postmortem orbitofrontal cortex of patients with major depressive disorder. *J. Neural Transm.* 110, 671–680.
- Yang, L., Mao, L., Tang, Q., Samdani, S., Liu, Z., and Wang, J.Q. (2004). A novel Ca^{2+} -independent signaling pathway to extracellular signal-regulated protein kinase by coactivation of NMDA receptors and metabotropic glutamate receptor 5 in neurons. *J. Neurosci.* 24, 10846–10857.
- Yuan, J.P., Kiselyov, K., Shin, D.M., Chen, J., Shcheynikov, N., Kang, S.H., Dehoff, M.H., Schwarz, M.K., Seeburg, P.H., Muallem, S., et al. (2003). Homer binds TRPC family channels and is required for gating of TRPC1 by IP3 receptors. *Cell* 114, 777–789.