The Role of Stress-Induced Changes of Homer1 Expression in Stress Susceptibility

Vasilii V. Reshetnikov1,2,a* and Natalia P. Bondar1,3

1Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russia
2Sirius University of Science and Technology, 354340 Sochi, Russia
3Department of Natural Sciences, Novosibirsk State University, 630090 Novosibirsk, Russia

e-mail: vasiliyreshetnikov@bionet.nsc.ru

Received October 5, 2020
Revised February 25, 2021
Accepted March 5, 2021

Abstract—Stress negatively affects processes of synaptic plasticity and is a major risk factor of various psychopathologies such as depression and anxiety. HOMER1 is an important component of the postsynaptic density: constitutively expressed long isoforms HOMER1b and HOMER1c bind to group I metabotropic glutamate receptors MGLUR1 (GRM1) and MGLUR5 and to other effector proteins, thereby forming a postsynaptic protein scaffold. Activation of the GLUR1–HOMER1b,c and/or GLUR5–HOMER1b,c complex regulates activity of the NMDA and AMPA receptors and Ca2+ homeostasis, thus modulating various types of synaptic plasticity. Dominant negative transcript Homer1a is formed as a result of activity-induced alternative termination of transcription. Expression of this truncated isoform in response to neuronal activation impairs interactions of HOMER1b,c with adaptor proteins, triggers ligand-independent signal transduction through MGLUR1 and/or MGLUR5, leads to suppression of the AMPA- and NMDA-mediated signal transmission, and thereby launches remodeling of the postsynaptic protein scaffold and inhibits long-term potentiation. The studies on animal models confirm that the Homer1a-dependent remodeling most likely plays an important part in the stress susceptibility, whereas Homer1a itself can be regarded as a neuroprotector. In this review article, we consider the effects of different stressors in various animal models on HOMER1 expression as well as impact of different HOMER1 variants on human behavior as well as structural and functional characteristics of the brain.

DOI: 10.1134/S0006297921060018

Keywords: stress, depression, synaptic plasticity, Homer1, metabotropic glutamate receptors

INTRODUCTION

Stress disrupts the balance between excitatory and inhibitory signals in the brain, which are mediated mainly by the changes in activity of the glutamatergic (excitatory) system and GABAergic (inhibitory) system. Disturbance of this balance leads to morphological changes and reorganization of the dendritic network in various brain structures [1]. Chronic deviations of the glutamate levels from the norm could play a key role in long-term structural and functional impairments of synaptic plasticity associated with various psychopathologies [2].

Abbreviations: AMPA receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; LTD, long-term depression; LTP, long-term potentiation; MGLUR, metabotropic glutamate receptor; MGLUR1/5, group I metabotropic glutamate receptors; NMDA receptor, N-methyl-D-aspartate glutamate receptor.

* To whom correspondence should be addressed.
homeostasis, long-term potentiation (LTP), and long-term depression (LTD) [17, 18]. Because the impaired glutamate transmission is observed in a variety of stress-induced psychopathologies, we have hypothesized that HOMER1 can be considered as an important component of stress susceptibility/resistance. Research in the last two decades indicates that changes in the expression of HOMER1 or its dominant negative isoform HOMER1a are observed in animals after restraint stress [19], social defeat stress [20], and in adult animals subjected to prenatal stress [21]. In addition, it has been shown that the expression of HOMER1 changes after treatment with anxiolytics or antidepressants [22]. Nonetheless, despite extensive investigation of the function of HOMER1 in synaptic plasticity, little is known about the role that the altered ratio of its isoforms plays in stress susceptibility and in stress-induced psychiatric disorders.

STRUCTURE OF HOMER1

HOMER1 has nine protein isoforms, three of them (HOMER1b, HOMER1c, and HOMER1d) are “long” isoforms that contain all functional domains, another two (HOMER1a and Ania3 [HOMER1m]) lack the C-terminal domain, and four isoforms (HOMER1e, -f, -g, and -h) partially or completely lack both functional domains [23]. In our review, we will focus on the four most studied isoforms (HOMER1a, HOMER1b, HOMER1c, and Ania3) because only these have been reported to have functional significance.

In neurons at rest, the Homer1 gene is transcribed into constitutively expressed transcripts Homer1b and/or Homer1c. Neuronal activation stimulates formation of the short transcripts Homer1a and Ania3, which are immediate early transcripts; and expression of these isoforms ensures adaptation to stress at the molecular level. The mechanism of the expression switch from the long to short transcripts is not fully elucidated and is believed to be related to premature stalling of RNA polymerase II, mRNA cleavage, and polyadenylation of the formed 3′-end [24]. It has been shown that the transcription factor MEF2 and the regulatory sequence TTGTTGGG (located near the site of transcription termination in short Homer1 transcripts) are important for this process [24].

HOMER1 contains a conserved region that includes the N-terminal EVH1 (WH1, RanBP1-WASP) domain, which binds to a consensus proline-rich sequence (Pro-Pro-X-X-Phe), as well as to the so-called proline motif (P-motif): a sequence of 5 amino acid residues (Ser-Pro-Leu-Thr-Pro) [23]. EVH1 binds to a variety of adaptor proteins, receptors, and ligands (see [18, 23] for review). P-motif can also bind to the EVH1 domain, but EVH1 binding to Pro-Pro-X-X-Phe is stronger [25]. Therefore, P-motif can bind to the neighboring EVH1 domains only in the absence of available Pro-Pro-X-X-Phe motifs, thus preventing multimerization of the HOMER1—receptor and/or HOMER1—effector protein complexes. Hence, P-motif is important for regulation of HOMER1 multimerization [25].

Additionally, the long isoforms (HOMER1b and HOMER1c) have a C-terminal coiled-coil (CC) domain, which mediates multimerization of these isoforms owing to the binding of specific motifs of the leucine zipper type to each other [26]. Isoforms HOMER1b and HOMER1c have similar structures and functions and differ only in a 12-amino-acid sequence, whose function is not fully understood (Fig. 1). Multimeric complexes of HOMER1b and/or HOMER1c (hereafter HOMER1b,c) are capable of binding to many different effector proteins, thus ensuring high velocity of synaptic transmission at the postsynaptic membrane. Transcripts Homer1a and Ania3 lack the sequence coding for the CC domain, while the 3′-untranslated region (3′-UTR) contains many AAUAAA repeats that are characteristic of early response genes [26, 27]. The presence of such repeats reduces mRNA stability and leads to its selective degradation [28]. The truncated transcripts contain 5-6 exons, in contrast to 10 in the full-length transcripts Homer1b and Homer1c. Homer1a and Ania3 differ from each other in the C-terminal amino acid sequence (Fig. 1), and functional significance of these dissimilarities remains unclear too. Nevertheless, it should be noted that the expression patterns of Homer1a and Ania3 mRNAs in response to neuronal activation are different: Homer1a mRNA expression reaches its peak within an hour, whereas Ania3 mRNA expression peaks only after 4 h [29].

The absence of the CC domain in the isoforms HOMER1a and Ania3 does not allow them to form oligomeric complexes with each other, while the presence of the EVH1 domain enables these isoforms to bind to proline-rich motifs of various receptors, including MGLUR1 and/or MGLUR5 and adaptor proteins. Thus, both short isoforms serve as dominant negative genetic factors by capturing molecules that target HOMER1b and HOMER1c and causing dissociation of the protein complexes involving HOMER1b,c on the postsynaptic membrane. Disruption of the HOMER1b,c links under the influence of HOMER1a leads to the decrease in the intracellular Ca2+ concentration [30] and to inhibition of the signal transduction pathways; both effects together contribute to postsynaptic-density remodeling. It should be pointed out that in many studies, short isoforms are not categorized into HOMER1a and Ania3, and the long ones into b and c; therefore, the functions of individual isoforms remain poorly investigated.

ROLE OF HOMER1 IN SYNAPTIC PLASTICITY

The speed and duration of synaptic transmission and ability of the cell to respond appropriately to external...
stimuli are integral characteristics of synaptic plasticity. Even though HOMER1 binds to many protein molecules, its most important role in synaptic plasticity is most likely related to its interaction with MGLUR1 and/or MGLUR5 [10, 17, 18, 26, 31]. Complexes MGLUR1–HOMER1b,c and/or MGLUR5–HOMER1b,c play an important part in various types of synaptic plasticity, such as LTP [32], LTD [33-35], or depotentiation [36]. It is worth noting that the molecular mechanism underlying MGLUR1- and/or MGLUR5-mediated initiation of LTP is similar to that of LTD, and, in all likelihood, whether LTP or LTD gets triggered is determined by the activity of other components of the system [32]. Canonical MGLUR1 and MGLUR5 signal transmission proceeds through phospholipase C activation by the Gqα subunit, which forms after dissociation of the heterodimeric complex of G proteins MGLUR1 and MGLUR5 as a result of ligand binding to the receptor (Fig. 2a) [37]. Phospholipase C catalyzes hydrolysis of phosphoinositides with formation of inositol-1,4,5-triphosphate (IP3) and diacylglycerol. IP3 binds to its receptors (IP3R) on the surface of endoplasmic reticulum and promotes Ca2+ release into the intracellular space; diacylglycerol, in turn, activates protein kinase C [38]. Both mechanisms underlie MGLUR1- and/or MGLUR5-mediated activation of signal transduction pathways via mitogen-activated kinase (MAPK), mTOR, and cAMP-CREB [38-40]. In addition, protein kinase C, just as Ca2+-induced kinase CAMK2B, directly phosphorylates C-terminus of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA receptor) subunits, thereby ensuring their stability on the postsynaptic membrane.

Agglomerates MGLUR1–HOMER1b,c and/or MGLUR5–HOMER1b,c are located at the periphery of the synapse, either in the perisynaptic region or embedded in the endoplasmic reticulum membrane [40, 41]. The multimeric HOMER1b,c complexes can form regulatory networks, such as MGLUR1/5–HOMER1b,c–Shank–GKAP–PSD95 through protein–protein interactions, the latter enhance efficiency of signal transduction through the N-methyl-D-aspartate glutamate receptor (NMDA receptors) and are structural components of the postsynaptic density [18, 42, 43]. Moreover, binding of the MGLUR1–HOMER1b,c and/or MGLUR5–HOMER1b,c complex to endoplasmic-reticulum IP3R...
ensures regulation of Ca$^{2+}$ homeostasis [44]. Hence, interaction with various adaptor proteins in the postsynaptic density as well as the fact that HOMER1b,c is required for maturation of dendritic spines [44-46] suggest that HOMER1b,c helps to provide the necessary “backbone” of the postsynaptic density.

The short isoform HOMER1a competes with HOMER1b,c for binding to adaptor proteins causing dissociation of the HOMER1b,c–Shank–GKAP–PSD95 agglomerates in a dose-dependent manner [42]. Furthermore, binding of HOMER1a to endoplasmic reticulum MGLUR1 and/or MGLUR5 leads to their transfer to the postsynaptic space [47], where they can directly inhibit signal transduction through the NMDA receptors via binding of the β-subunit of the MGLUR1 or MGLUR5 receptor G protein to the C-terminus of the NR1 subunit of NMDA receptor [48, 49]. Increase in the HOMER1a expression and disruption of interactions HOMER1b,c–MGLUR1 and HOMER1b,c–MGLUR5 launch the ligand-independent activation of MGLUR1 and/or MGLUR5 [17, 47, 50]. This activation causes decrease in the number of AMPA receptors on the postsynaptic membrane owing to the reduced phosphorylation of the GLUA2 subunit of AMPA receptors and their increased endocytosis (see detailed review of the mechanism in [17, 18, 50, 51]). The HOMER1a-induced reduction of the efficiency of synaptic transmission via MGLUR1 and MGLUR5 provides the basis for the so-called homeostatic synaptic plasticity, which is aimed at maintaining long-term stability of molecular networks [52]. Consequently, HOMER1a overexpression leads to remodeling of the postsynaptic density. Functionally,
these changes are accompanied by LTP suppression and contribute to the decrease in synaptic-transmission efficiency [53, 54] and to the reduction in the synapse size and in the number of mature spines on a dendrite [46]. In contrast, some studies indicate that HOMER1a expression enhances synaptic transmission due to the glutamate-independent MGLUR5-mediated increase in the expression and in the number of AMPA receptors on the postsynaptic membrane [55, 56]. The mechanism behind such activation of glutamatergic transmission is not clear because it was demonstrated in [56] and in other previous studies that the increased expression of HOMER1a induced dephosphorylation of the AMPA receptor subunits. It is assumed that dephosphorylation leads to the decrease in the number of AMPA receptors on the postsynaptic membrane [57]. Therefore, we believe that the claim that the enhanced expression of HOMER1a results in the increase of AMPA-mediated signaling requires further verification. It is possible that the effects observed in these studies were caused by methodological details associated with the increase of the HOMER1a content. In particular, in the study [56] HOMER1a was synthesized in bacterial cells and delivered into neurons as part of the TAT–HOMER1a protein construct. We presume that this method of delivery of HOMER1a into the cell could distort its effects on synaptic plasticity due to the fact of selective transport of HOMER1a only in some of the numerous different synapses [58].

ACUTE STRESS INDUCES HOMER1A EXPRESSION

Acute stress leads to neuronal activation and significantly raises the speed of Homer1 transcription initiation with formation of the short transcripts Homer1a and Ania3 [27]. It has been reported that acute stress in the contextual fear conditioning test results in a persistent increase in the Homer1a expression in various regions of the hippocampus and amygdala; this change was observed already 30 min after the stress and persisted for up to 24 h [59, 60] (table). The stress caused by a predator fear also induces expression of the Homer1a transcript in various brain regions such as hippocampus, hypothalamus, and amygdala [61]. Moreover, the level of Homer1a expression in these brain structures correlates with the duration of the freezing reaction [61]. Similar changes were observed after a single exposure to social defeat stress in the adult male C57BL mice; these alterations did not lead to upregulation of the Homer1a transcript by itself but decreased the levels of transcripts Homer1b and Homer1c (and probably changed the Homer1a/Homer1b/Homer1c ratio) in the dorsal hippocampus and were accompanied by impaired spatial memory [20]. On the other hand, these negative effects of stress on spatial memory were neutralized either by the targeted overexpression of transcripts Homer1b and Homer1c in the dorsal hippocampus or by administration of the MGLUR5 antagonist (3-2-methyl-4-thiazolyl-ethynyl-pyridine, MTEP) 5 min before the initiation of the social defeat stress [20]. In rats shocked with an electric current (foot shock), Homer1b and Homer1c expression in the prefrontal cortex was found to be reduced 24 h after the exposure [62]. In general, induction of the HOMER1a isoform expression regardless of the type of stress is in good agreement with the results of other studies, which have shown that Homer1a induction is observed in response to various types of stimuli, such as chemically induced neuronal depolarization, epileptic activity, physical injury, administration of psychostimulants, physical activity, and the stress caused by adverse environmental factors or new environment (for review see [18, 22]). It can be concluded that the induction of HOMER1a expression during acute stress is nonspecific and probably takes part in the LTP suppression and in postsynaptic-density remodeling.

PARTICIPATION OF HOMER1 IN ADAPTATION TO CHRONIC STRESS

Chronic stress also affects the levels of expression of various HOMER1 isoforms. For instance, in rats subjected to chronic restraint stress (6 h/day for 21 days), the amounts of isoforms HOMER1b and -c [63] and the levels of their mRNAs [19] increased in the hippocampus 18 h after the last exposure to stress. Similar changes in the expression of Homer1b and -c in the dorsal hippocampus were observed after chronic social defeat stress [64]. In addition, it was demonstrated in [64] that chronic social defeat stress decreased the number of HOMER1b,c complexes with MGLUR5 as compared to the control group, although the amounts of HOMER1b, HOMER1c, and MGLUR5 were similar between the groups. An elegant study on mice [65] has revealed that animals susceptible to chronic social defeat stress and animals subjected to chronic restraint stress displayed similar increase in the mRNA and protein expression of HOMER1b and HOMER1c in the hippocampus, regardless of the type of stress. In that study, expression levels of HOMER1b and HOMER1c negatively correlated with the parameters of social behavior (social interaction ratio) and positively correlated with the parameter of depressive-like behavior (sucrose preference), which were assessed in these animals after exposure to chronic stress. Besides, the authors of that study demonstrated that in animals susceptible to chronic social defeat stress, there was enhancement of the MGLUR–HOMER1b,c-mediated LTD and reduced expression of the AMPA receptor subunits (GLUA1 and GLUA2). Accordingly, those authors suggest that the increase in the MGLUR–HOMER1b,c-mediated signaling drives Ca²⁺ release from endoplasmic reticulum, and this Ca²⁺ activates PERK–eIF2α and the
| Species (strain) | Age/sex during stress | Stressor type | Stress duration | Timing of sampling | Brain structure | Method | Expression of HOMER1 | Reference |
|-----------------|-----------------------|---------------|-----------------|-------------------|----------------|--------|----------------------|----------|
| Rats (Lister hooded) | adults ♂ | contextual fear conditioning | one-time | in 30 min; 1 h; 4 h; 24 h | areas CA1, DG dHIP (∼3.5 mm relative to Bregma) | in situ | Homer1b and Homer1c unchanged in all tested regions; Homer1a ↑ in CA1 in 30 min, 2, and 4 h; ↑ in DG in 30 min; Ania3 ↑ in CA1, CA3 and DG in 30 min | [59] |
| Mice (C57BL/6J) | adults (6-10 w) ♂ | contextual fear conditioning | one-time | in 2 h | HIP; AMY | qPCR | Homer1a ↑ both in HIP and in AMY; Homer1c unchanged | [60] |
| Rats (Sprague–Dawley) | adults ♂ | exposure to predator | one-time for 15 min | in 1 h | PVN (Bregma −1.80 mm); AMY, DG, CA1, CA3 (Bregma −3.14 mm) | in situ | Homer1a ↑ in all brain structures | [61] |
| Mice (C57BL/6N) | adults (12 w) ♂ | social defeat stress | one-time for 5 min | in 1 h; 4 h; 8 h; 24 h | CA1 area of HIP | in situ | Homer1a unchanged at any time point; Homer1b and/or -c ↓ in 4 and 8 h | [20] |
| Rats (Sprague–Dawley) | adults ♂ | foot shock | 40 min | in 1 d; 7 d; 14 d | HIP | qPCR; Western blotting | protein HOMER1 ↑ in 7 days, Homer1b and -c = | [105] |
| Rats (Sprague–Dawley) | adults ♂ | foot shock | 40 min | in 24 h; 7 d; 14 d | mPFC | qPCR | Homer1b and/or -c ↓ in 24 h | [62] |
| Rats (Wistar) | adults ♂ | restraint stress | repeated at 6 h/d for 21 d | in 18 h | HIP | Western blotting | HOMER1b and/or -c ↑ | [63] |
| Rats (Wistar) | adults ♂ | restraint stress | repeated at 6 h/d for 21 d | in 18 h | HIP | qPCR | Homer1b and/or -c ↑ | [19] |
| Mice (C57BL/6N) | adults (12 w) ♂ | social defeat stress | repeated once a day for 21 d | in 24 h | DG, CA1, CA3 areas of dHIP | in situ | Homer1b and/or -c ↑ in CA1, CA3; Homer1a unchanged | [64] |
| Mice (C57BL/6J) | adults (7-8 w) ♂ | social defeat stress; restraint stress | repeated once a day for 10 d; repeated at 2 h/d for 21 d | in 120 h; 72 h | mPFC, HIP, AMY, HIP | qPCR; Western blotting | HOMER1b and/or -c ↑ in HIP in animals susceptible to social defeat stress; HOMER1a unchanged; HOMER1b and/or -c ↑ HIP | [65] |
| Rats (Wistar) | adults (weight 170 g) ♂ | chronic mild stress | repeated for 42 d | n/a | FC | qPCR | Homer1b and/or -c ↓ | [68] |
| Rats (Wistar) | adolescents (5-6 w) ♂ | chronic mild stress | repeated for 56 d | n/a | mPFC | proteomics | HOMER1b and/or -c ↑ | [69] |
| Mice (C57BL/6J) | adults (8-10 w) ♂ | chronic mild stress | repeated for 57 d | in 120 h | HIP; PFC | Western blotting | HOMER1a ↓ in HIP and PFC | [66] |
| Mice (C57BL/6J) | adults (15-16 w) ♂ | social defeat stress; combination of early postnatal stress and social defeat stress at adult age | social defeat stress once a day for 15 d; early postnatal: separation of pups from mothers for 3 h once a day from postnatal day 2 to postnatal day 14 | at 48 h after last social confrontation | PFC | RNA-seq; qPCR | Homer1a ↓ in combined-stress group | [67] |
CREB signaling pathway in the hippocampus (the amounts of phosphorylated forms of PERK, eIF2α, and CREB are higher in the group susceptible to stress). Similar effects have been reported in the model of chronic mild stress, which downregulated HOMER1a in the hippocampus and prefrontal cortex, and this decrease was accompanied by the pronounced depression-like phenotype in the animals [66]. The prolonged exposure to high-frequency transcranial magnetic stimulation (15 or 25 Hz from day 30 to day 57 of stress), which stimulates the activity of brain neurons and is used in the treatment of various neurological and mental disorders, attenuates the effects of stress both on behavior and on HOMER1a expression in various brain structures [66]. Given that HOMER1a is known to be a dominant negative isoform, it can be assumed that the decrease in its amount enhances HOMER1b,c-mediated signaling. The similar decrease in Homer1 expression in the prefrontal cortex of adult male mice exposed to chronic social defeat stress and explained mainly by downregulation of HOMER1a expression was noted in our work [67].

Nonetheless, not all brain structures show similar effects of chronic stress on the HOMER1a/HOMER1b/HOMER1c ratio. In the abovementioned study [65], the animals exposed to chronic social defeat stress manifested changes in the expression of HOMER1b and HOMER1c only in the hippocampus, while the levels of HOMER1b, HOMER1c, and HOMER1a remained unchanged in the prefrontal cortex and amygdala. Chronic mild stress for six weeks led to the decrease in

| Species (strain) | Age/sex during stress | Stressor type | Stress duration | Timing of sampling | Brain structure | Method | Expression of HOMER1 | Reference |
|-----------------|-----------------------|--------------|----------------|-------------------|----------------|-------|---------------------|-----------|
| Mice (C57BL/6J) | adults (12-15 w) ♀ | early postnatal stress | separation of pups from mothers for 15 or 180 min once a day from postnatal day 2 to postnatal day 14 | at adult age | dHIP (Bregma –1.86 to –2.16 mm); PFC | qPCR | Homer1a = in both groups; Homer1b and -c = in both groups | [74] |
| Mice (C57BL/6J) | adults (12-15 w) ♀ | early postnatal stress | separation of pups from mothers for 180 min once a day from postnatal day 2 to postnatal day 14; one-time separation from mothers for 24 h on postnatal day 9 | at adult age | PFC | RNA-seq | in chronic postnatal stress group: Homer1 ↓, but Homer1a and Homer1b and -c unchanged individually; in one-time separation group: Homer1, Homer1a, Homer1b and -c = | unpublished results, NCBI BioProject PRJNA649640 |
| Mice (C57BL/6J) | pups (15 d) ♀ | early postnatal stress | separation of pups from mothers for 180 min once a day from postnatal day 2 to postnatal day 14; one-time separation from mothers for 24 h on postnatal day 9 | on postnatal day 15 | PFC | RNA-seq | both in one-time separation group and in repeated separation group: Homer1, Homer1a, Homer1b and -c = | unpublished results, NCBI BioProject PRJNA649640 |
| Rats (Sprague-Dawley) | juveniles (21 d) ♀ | prenatal stress combined with restraint stress for mothers | repeated (3 times a day for 30 min during last 7 d of gestation) | on postnatal day 21 | AMY, HIP, PFC | Western blotting | HOMER1a ↑ in AMY, HIP, and PFC; HOMER1b and/or -c ↑ in PFC | [73] |
| Rats (Sprague-Dawley) | adults (17 w) ♀ | prenatal stress combined with restraint stress for mothers | repeated (3 times a day for 45 min starting from day 11 of pregnancy) | at adult age | AMY, dHIP; PFC | in situ | Homer1a ↑ in AMY and ↓ in HIP and PFC; Homer1b and/or -c ↓ in AMY | [21] |

Notes. PVN, paraventricular nuclei of the hypothalamus; AMY, amygdala; FC, frontal cortex; HIP, hippocampus; dHIP, dorsal hippocampus; PFC, prefrontal cortex; mPFC, medial prefrontal cortex; qPCR, quantitative PCR; RNA-seq, high-throughput RNA sequencing; ↑, increased expression; ↓, decreased expression; =, unchanged expression; N/A, no data.
Homer1b and Homer1c levels in the frontal cortex [68]. Besides, proteomic analysis revealed that the HOMER1b and HOMER1c levels in the prefrontal cortex are higher in the rats resistant to chronic mild stress, than in the susceptible animals [69]. It can be suggested that such differences in the effects of chronic stress on HOMER1 could be related to the region specificity of these phenomena, methodological differences, the type of stress, and different methods for protein quantitation. We can conclude that the most reproducible effects of various types of chronic stress involve upregulation of HOMER1b,c and decrease in the HOMER1a/HOMER1b/HOMER1c ratio in hippocampus, and these molecular changes are directly related to the susceptibility/resistance of animals to chronic stress.

**DIRECT EFFECTS OF STRESS ON HOMER1 EXPRESSION**

Stress early in life (prenatal and early postnatal periods) can affect stress susceptibility in adolescence and adulthood. Molecular mechanisms underlying these delayed effects of stress are most likely associated with epigenetic changes that alter the pattern of gene expression [70, 71]. Homer1a expression in cortical structures and in hippocampus increases gradually after birth and reaches peak in the 3rd postnatal week in rodents [31, 72]. This process coincides with the period of intense reorganization of synapses and establishment of the stable synaptic networks. In a study on rats, it was found that chronic stress during prenatal period increased mRNA expression in the hippocampus and prefrontal cortex was demonstrated by the finding that the carriers of rs7713917 polymorphism in the HOMER1 gene [78, 79], and there are similar reports regarding suicidal behavior [80, 81]. Functional significance of such polymorphisms is still not fully understood; however, investigators have been able to predict possible transcription factor-binding sites (e.g., for CEBPA, REL, and NFKB1) that can be disrupted by polymorphic substitutions using various bioinformatic approaches [79, 81].

**DELAYED EFFECTS OF STRESS ON HOMER1 EXPRESSION**

Stress early in life (prenatal and early postnatal periods) can affect stress susceptibility in adolescence and adulthood. Molecular mechanisms underlying these delayed effects of stress are most likely associated with epigenetic changes that alter the pattern of gene expression [70, 71]. Homer1a expression in cortical structures and in hippocampus increases gradually after birth and reaches peak in the 3rd postnatal week in rodents [31, 72]. This process coincides with the period of intense reorganization of synapses and establishment of the stable synaptic networks. In a study on rats, it was found that chronic stress during prenatal period increased mRNA expression in the hippocampus and prefrontal cortex was demonstrated by the finding that the carriers of rs7713917 polymorphism in the HOMER1 gene [78, 79], and there are similar reports regarding suicidal behavior [80, 81]. Functional significance of such polymorphisms is still not fully understood; however, investigators have been able to predict possible transcription factor-binding sites (e.g., for CEBPA, REL, and NFKB1) that can be disrupted by polymorphic substitutions using various bioinformatic approaches [79, 81]. Functional magnetic resonance imaging data have shown that the presence of the rs7713917 polymorphism in humans results in the decreased activation of the prefrontal cortex during expectation of a reward [78] and in increased activation in response to emotional stimulus [82]. These data probably mean reduced level of motivation and increased impulsivity. Furthermore, carriers of this allele switch attention more slowly in response to negative stimuli, possibly indicating an anomaly in the processes of executive control [83]. Aside from the functional changes in carriers of the risk allele (A) of rs7713917, the volume of the medial prefrontal cortex proved to be smaller in these individuals, and indicators of fractional anisotropy in the frontal tract were found to be reduced [82]. Such structural features are suggestive of a myelination decrease, which is often associated with the stress-induced mental disorders [84]. It must be mentioned that the results of postmortem studies show no changes in the HOMER1 expression between those who were depressed when alive and those who were not depressed; only recently, a study revealed that the HOMER1a level in interneurons of the striatum is higher in the depressed patients compared with the nominally healthy individuals [85]. On the other hand, the region-specific changes in the expression of MGLUR1 and MGLUR5 are often detectable in the depressed individuals [5, 86], which may also indicate aberration of the HOMER1-mediated signaling. Furthermore, the importance of HOMER1 in resistance to mental illness is confirmed by the finding that the carriers of HOMER1 risk alleles are less responsive to the treatment with antidepressants [82, 87].

**GENETIC VARIANTS OF HOMER1 ASSOCIATED WITH THE DEVELOPMENT OF DEPRESSION AND OTHER MENTAL DISORDERS**

The data obtained in the genome-wide association studies point to the link between depression and some polymorphisms in the regulatory regions of the HOMER1 gene [78, 79], and there are similar reports regarding suicidal behavior [80, 81]. Functional significance of such polymorphisms is still not fully understood; however, investigators have been able to predict possible transcription factor-binding sites (e.g., for CEBPA, REL, and NFKB1) that can be disrupted by polymorphic substitutions using various bioinformatic approaches [79, 81]. Functional magnetic resonance imaging data have shown that the presence of the rs7713917 polymorphism in humans results in the decreased activation of the prefrontal cortex during expectation of a reward [78] and in increased activation in response to emotional stimulus [82]. These data probably mean reduced level of motivation and increased impulsivity. Furthermore, carriers of this allele switch attention more slowly in response to negative stimuli, possibly indicating an anomaly in the processes of executive control [83]. Aside from the functional changes in carriers of the risk allele (A) of rs7713917, the volume of the medial prefrontal cortex proved to be smaller in these individuals, and indicators of fractional anisotropy in the frontal tract were found to be reduced [82]. Such structural features are suggestive of a myelination decrease, which is often associated with the stress-induced mental disorders [84]. It must be mentioned that the results of postmortem studies show no changes in the HOMER1 expression between those who were depressed when alive and those who were not depressed; only recently, a study revealed that the HOMER1a level in interneurons of the striatum is higher in the depressed patients compared with the nominally healthy individuals [85]. On the other hand, the region-specific changes in the expression of MGLUR1 and MGLUR5 are often detectable in the depressed individuals [5, 86], which may also indicate aberration of the HOMER1-mediated signaling. Furthermore, the importance of HOMER1 in resistance to mental illness is confirmed by the finding that the carriers of HOMER1 risk alleles are less responsive to the treatment with antidepressants [82, 87].
The data presented so far indicate that acute stress mostly increases HOMER1a expression in various regions of the brain, whereas chronic stress most often upregulates isoforms HOMER1b and/or HOMER1c in the hippocampus. It is noteworthy that these changes in the HOMER1a/HOMER1b/HOMER1c ratio in the hippocampus or prefrontal cortex can determine resistance or susceptibility to stress [65, 67]. These data are in good agreement with the previous studies demonstrating that the induction of Homer1a in the cortical structures allows better adaptation to stressful conditions [88] and has a pronounced antidepressant effect [22, 89-91]. Moreover, increase in the Homer1a expression is observed during treatment with various pharmaceuticals [22] and during treatment with other modalities, such as transcranial magnetic stimulation [89], electroconvulsive therapy [91], sleep deprivation [91], or phototherapy [90].

Fig. 3. Putative role of Homer1a-dependent remodeling in stress resistance and in synaptic transmission. a) Reversible repression (downscaling) of synaptic transmission occurs with strong upregulation of HOMER1a (↑↑↑) in response to LTP, which is necessary to protect the cell from excessive activation of glutamatergic transmission and to adapt the cell to subsequent LTP. This pattern is typical for stress-resistant individuals or for individuals exposed to short-term stress. b) HOMER1a-dependent activity reduction (downscaling) is observed in response to LTP only in some synapses with weak Homer1a upregulation (↑), while other synapses continue to be in the LTP state, after which an LTD phase inevitably begins, which is accompanied by deeper inhibition of synaptic transmission. This pattern is characteristic for stress-susceptible individuals and individuals under chronic stress.

Meanwhile, the data on the delayed effects of stress in animals suggest that behavioral disturbances and increased susceptibility to stress may be related to the changes in the total expression of Homer1 rather than to the altered Homer1a/Homer1b/Homer1c ratio. Nevertheless, we could hypothesize that it is the delay of Homer1a induction that is causing negative effects on behavior because the specific action of this short isoform has been associated with the resistance to stress. Support of our hypothesis could be found in the studies of Homer1 knockout animals, which exhibit decreased exploratory activity, increased anxiety, impaired adaptive behavior in the forced swimming test, and impaired sensorimotor reactions and cognitive functions [92, 93]. On the other hand, restoration of the expression of only the Homer1a isoform in the prefrontal cortex by means of a vector construct eliminates most of the negative effects on behavior observed in these animals [93]. By contrast, restoration of the Homer1b and/or Homer1c expression in the prefrontal cortex does not lead to any behavioral improvement.

What are molecular mechanisms of these effects of HOMER1a? There is no exact answer to date. Given that
HOMER1b,c can modulate various forms of synaptic plasticity, but in contrast, HOMER1a does not drive remodeling of the postsynaptic density; it can be assumed that the effects of these isoforms cannot be explained by altered synaptic-transmission velocity alone. Recent reports suggest that the antidepressant action of the Homer1a induction is explained by the activation of the ERK signaling cascade, both through the BDNF–Ras–ERK and A1R–ERK1/2 pathways [22]. Another work [65] indicates that the increased susceptibility to stress is related to the PERK-eIF2α pathway activity in the hippocampus. It must be pointed out that the Homer1a induction in different brain structures, such as prefrontal cortex and hippocampus, could play opposite roles in the stress-induced depressive behavior [94]. Moreover, the impact of Homer1a on stress susceptibility may also depend on the degree of specificity of Homer1a expression induction (on whether it is activated specifically in only one brain region or in several at once) [95].

Interestingly enough, the suppression of LTP and of synaptic transmission under the effect of Homer1a induction is not exactly consistent with the generally accepted concept of a stress-induced biphasic change in the glutamatergic transmission activity [96–98]. This concept implies that acute stress enhances the glutamate release and incorporation of AMPA and NMDA receptors into the postsynaptic membrane, whereas chronic stress is associated with the decrease in the number of glutamate receptors on the postsynaptic membrane and with suppression of the glutamate signal transduction. Possible explanations for the discrepancy in the effects of Homer1a expression activation on AMPA receptor signaling could be different time profiles of the stress response [99] and the so-called biphasic remodeling of postsynaptic-membrane architecture [100]. The latter suggests that the prolonged stimulation with glutamate leads initially (after 30-60 min) to disruption of the Homer1b,c-containing postsynaptic clusters, but increase in the density of such clusters is observed (relative to baseline) 4-8 h after. In this context, the Homer1a-dependent remodeling can be regarded as an important participant in the “switching” of synaptic transmission, whereas Homer1a induction can be considered as a cell adaptation to aberrant activation of glutamatergic transmission; thus, Homer1a can play a neuroprotective role. The results of in vitro studies on neuronal cultures have revealed that Homer1a protects neurons from NMDA-mediated damage, which speaks in favor of such suggestion [101]. Furthermore, both overexpression of Homer1a and downregulation of Homer1b and/or Homer1c suppress apoptosis in the neurons subjected to traumatic treatments, enhance cell viability, and stimulate autophagy processes [102, 103]. The importance of Homer1a as a neuroprotective agent is also confirmed by the observation that it plays a considerable part in the homeostatic synaptic plasticity during sleep; this plasticity includes removal of AMPA receptors from the postsynaptic membrane and LTP inhibition, which results in the decrease in the number of excitatory synapses [104]. Nonetheless, although Homer1a causes suppression of LTP, the Homer1a-mediated changes of suppression of synaptic transmission (downscaling) are reversible and less pronounced in comparison with LTD or depotentiation [36].

Therefore, apparently, the possibility of rapid adaptation of synapses due to the Homer1a-dependent remodeling of postsynaptic density in response to various stimuli facilitates stability and prevention of the stronger inhibition of synaptic transmission in the neural networks (Fig. 3) responsible for the psycho-emotional state. In this context, upregulation of Homer1b and/or Homer1c expression induced by chronic stress may be a consequence rather than cause of the reduced glutamatergic signaling and the level of the activity-induced Homer1a expression.

**Funding.** This work was financially supported by the Russian Science Foundation (grant no. 16–15-10131).

**Ethics declarations.** The authors declare no conflicts of interest in financial or any other sphere. This article does not contain any studies with human participants or animals performed by any of the authors.

**Open access.** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

**REFERENCES**

1. Qiao, H., Li, M. X., Xu, C., Chen, H. B., An, S. C., and Ma, X. M. (2016) Dendritic spines in depression: what we learned from animal models, *Neural Plast.*, 2016, 8056370, doi: 10.1155/2016/8056370.
2. Musazzi, L., Treccani, G., and Popoli, M. (2015) Functional and structural remodeling of glutamate synapses in prefrontal and frontal cortex induced by behavioral stress, *Front. Psychiatry*, 6, 60, doi: 10.3389/Fpsyt.2015.00060.
3. Sanacora, G., Treccani, G., and Popoli, M. (2012) Towards a glutamate hypothesis of depression: an emerging frontier
of neuropsychopharmacology for mood disorders, *Neuropsychopharmacology*, **62**, 63-77, doi: 10.1016/j.neuropsychopharmacology.2011.07.036.

4. Gulyaeva, N. V. (2017) Interplay between brain BDNF and glutamatergic systems: a brief state of the evidence and association with the pathogenesis of depression, *Biochemistry (Moscow)*, **82**, 301-307, doi: 10.1134/S0006297917030087.

5. Deschwanden, A., Karolewicz, B., Feyissa, A. M., Treyer, V., Ametamey, S. M., et al. (2011) Reduced metabotrophic Glutamate receptor 5 density in major depression determined by [C-11]APB688 positron emission tomography and postmortem study, *Curr. Neuropharmacol.*, **9**, 15-15.

6. Tsai, G. C., and Coyle, J. T. (2002) Glutamatergic mechanisms in schizophrenia, *Annu. Rev. Pharmacol. Toxicol.*, **42**, 165-179, doi: 10.1146/annurev.pharmtox.42.082701.160735.

7. Engmann, O., Hortobágyi, T., Pidsley, R., Troakes, C., Bernstein, H. G., et al. (2011) Molecular evidence of synaptic pathology in the CA1 region in schizophrenia, *Brain Res.*, **1344**, 2408-2421, doi: 10.1016/j.brainres.2010.03.010.

8. Matosin, N., Fernandez-Enright, F., Lum, J. S., Engel, M., Andrews, J. L., et al. (2016) Functional interaction of phospholipase C-beta 3 with Shank2 and own proline-rich motif and links group 1 metabotropic glutamate receptors with IP3 receptors, *Neuron*, **21**, 717-726, doi: 10.1016/j.neuron.2016.02.011.

9. Fatemi, S. H., Folsom, T. D., Kneeland, R. E., Yousefi, M. K., Liesch, S. B., and Theras, P. D. (2013) Impairment of fragile X mental retardation protein-metabotropic glutamate receptor 5 signaling and its downstream cognates ras-related C3 botulinum toxin substrate 1, amyloid beta A4 precursor protein, striatal-enriched protein tyrosine phosphatase, and homer 1, in autism: a postmortem study in cerebellar vermis and superior frontal cortex, *Mol. Autism*, **4**, 21, doi: 10.1186/2040-2392-4-21.

10. Tu, J. C., Xiao, B., Yuan, J. P., Lanahan, A. A., Leoffert, K., et al. (1998) Homer binds a novel proline-rich motif and links group 1 metabotropic glutamate receptors with IP3 receptors, *Neuron*, **21**, 717-726, doi: 10.1016/S0896-6273(00)80589-9.

11. Nakamura, M., Sato, K., Fukaya, M., Araishi, K., Aiba, A., et al. (2004) Signaling complex formation of phospholipase C beta 4 with metabotropic glutamate receptor type 1 alpha and 1,4,5-trisphosphate receptor at the presynapse and endoplasmic reticulum in the mouse brain, *Eur. J. Neurosci.*, **20**, 2929-2944, doi: 10.1111/j.1460-9568.2004.03768.x.

12. Hwang, J. I., Kim, H. S., Lee, J. R., Kim, E., et al. (2005) The interaction of phospholipase C-beta 3 with Shank2 regulates mGluR-mediated calcium signal, *J. Biol. Chem.*, **280**, 12467-12473, doi: 10.1074/jbc.M410740200.

13. Yuan, J. P., Kiselyov, K., Shin, D. M., Chen, J., Shcheynikov, N., et al. (2003) Homer binds TRPC family channels and is required for gating of TRPC1 by IP3 receptors, *Cell*, **114**, 777-789, doi: 10.1016/S0092-8674(03)00716-5.

14. Kim, J. Y., Zeng, W. Z., Kiselyov, K., Yuan, J. P., Dephoff, M. H., et al. (2006) Homer 1 mediates store- and inositol 1,4,5-trisphosphate receptor-dependent translocation and retrieval of TRPC3 to the plasma membrane, *J. Biol. Chem.*, **281**, 32540-32549, doi: 10.1074/jbc.M602496200.

15. Hwang, S. Y., Wei, J., Westhoff, J. H., Duncan, R. S., Ozawa, F., et al. (2003) Differential functional interaction of two Vsl/Homer protein isoforms with ryanodine receptor type 1: a novel mechanism for control of intracellular calcium signaling, *Cell Calcium*, **34**, 177-184, doi: 10.1016/S0143-4160(03)00082-4.

16. Yamamoto, K., Sakagami, Y., Sugira, S., Inokuchi, K., Shimohama, S., and Kato, N. (2005) Homer 1 enhances spike-induced calcium influx via L-type calcium channels in neocortex pyramidal cells, *Eur. J. Neurosci.*, **22**, 1338-1348, doi: 10.1111/j.1460-9568.2005.04278.x.

17. Hu, J. H., Park, J. M., Park, S., Xiao, B., Dephoff, M. H., et al. (2010) Homeostatic scaling requires group I mGluR activation mediated by Homer1a, *Neuron*, **68**, 1128-1142, doi: 10.1016/j.neuron.2010.11.008.

18. Clifton, N. E., Trent, S., Thomas, K. L., and Hall, J. (2019) Regulation and function of activity-dependent homer in synaptic plasticity, *Mol. Neuropsychiatry*, **5**, 147-161, doi: 10.1159/000500267.

19. Orłowski, D., Elfving, B., Müller, H. K., Wegener, G., and Bjarkam, C. R. (2012) Wistar rats subjected to chronic restraint stress display increased hippocampal spine density paralleled by increased expression levels of synaptic scaffolding proteins, *Stress*, **15**, 514-523, doi: 10.3109/10253890.2011.643516.

20. Wagner, K. V., Hartmann, J., Mangold, K., Wang, X. D., Labermaier, C., et al. (2013) Homer1 mediates acute stress-induced cognitive deficits in the dorsal hippocampus, *J. Neuroscience*, **33**, 3857-3864, doi: 10.1523/JNEUROSCI.4333-12.2013.

21. Buonaguro, E. F., Morley-Fletcher, S., Avagliano, C., Vellucci, L., Iasevoli, F., et al. (2020) Glutamatergic postsynaptic density in early life stress programming: Topographic gene expression of mGlur5 receptors and Homer proteins, *Prog. Neuro Psychoph.*, **96**, 109725, doi: 10.1016/j.pnpbp.2019.109725.

22. Serchov, T., Heumann, R., van Calker, D., and Biber, K. (2016) Signaling pathways regulating Homer1a expression: implications for antidepressant therapy, *Biol. Chem.*, **397**, 207-214, doi: 10.1515/hbz-2015-0267.

23. Shiraishi-Yamaguchi, Y., and Furuichi, T. (2007) The Homer family proteins, *Genome Biol.*, **8**, 206, doi: 10.1186/Gb-2007-8-2-206.

24. Flavell, S. W., Kim, T. K., Gray, J. M., Harmin, D. A., Hemberg, M., et al. (2008) Genome-wide analysis of MEF2 transcriptional program reveals synaptic target genes and neuronal activity-dependent polyadenylation site selection, *Neuron*, **60**, 1022-1038, doi: 10.1016/j.neuron.2008.11.029.

25. Irie, K., Nakatsu, T., Mitsuoka, K., Miyazawa, A., Sobue, K., et al. (2002) Crystal structure of the homer 1 family conserved region reveals the interaction between the EVH1 domain and own proline-rich motif, *J. Mol. Biol.*, **318**, 1117-1126, doi: 10.1016/S0022-2836(02)00170-5.

26. Xiao, B., Tu, J. C., Petralia, R. S., Yuan, J. P., Doan, A., et al. (1998) Homer regulates the association of group 1 metabotropic glutamate receptors with multivalent complexes of Homer-related, synaptic proteins, *Neuron*, **21**, 707-716, doi: 10.1016/S0896-6273(00)50858-7.

27. Bottai, D., Guzowski, J. F., Schwarz, M. K., Kang, S. H., Xiao, B., et al. (2002) Synaptic activity-induced conversion of intronic to exonic sequence in Homer 1 immediate early gene expression, *J. Neuroscience*, **22**, 167-175, doi: 10.1523/JNEUROSCI.22-01-00167.2002.

28. Shaw, G., and Kamen, R. (2012) A conserved AU sequence in the 3’ untranslated region of GM-CSF mRNA medi-
iates selective mRNA degradation, *J. Immunol.*, **189**, 5-13.

29. Hermy, G., Mahlke, C., Gutzmann, J. J., Schreiber, J., Bluthgen, N., and Kuhl, D. (2013) Genome-wide profiling of the activity-dependent hippocampal transcriptome, *PLoS One*, **8**, e67903, doi: 10.1371/journal.pone.0067903.

30. Worley, P. F., Zeng, W. Z., Huang, G. J., Kim, J. Y., Shin, D. M., et al. (2007) Homer proteins in Ca²⁺ signaling by excitable and non-excitable cells, *Cell Calcium*, **42**, 363-371, doi: 10.1016/j.cca.2007.05.007.

31. Brakeman, P. R., Lanahan, A. A., O’Brien, R., Roche, K., Barnes, C. A., et al. (1997) Homer: a protein that selectively binds metabotropic glutamate receptors, *Nature*, **386**, 284-288, doi: 10.1038/386284a0.

32. Le Duigou, C., and Kullmann, D. M. (2011) Group I mGluR agonist-evoked long-term potentiation in hippocampal oriens interneurons, *J. Neuroscience*, **31**, 5777-5781, doi: 10.1523/Jneurosci.6265-10.2011.

33. Ronesi, J. A., and Huber, K. M. (2008) Homer interactions are necessary for metabotropic glutamate receptor-induced long-term depression and translational activation, *J. Neuroscience*, **28**, 543-547, doi: 10.1523/JNEUROSCI.0707-08.2008.

34. Bellone, C., Lüscher, C., and Mameli, M. (2008) Mechanisms of synaptic depression triggered by metabotropic glutamate receptors, *Cell. Mol. Life Sci.*, **65**, 2913-2923, doi: 10.1007/s00018-008-8263-3.

35. Lüscher, C., and Huber, K. M. (2010) Group I mGluR-dependent synaptic long-term depression: mechanisms and implications for circuitry and disease, *Neuron*, **65**, 445-459, doi: 10.1016/j.neuron.2010.01.016.

36. Jones, O. D. (2017) Do group I metabotropic glutamate receptors mediate LTD? *Neurobiol. Learn Mem.*, **138**, 85-97, doi: 10.1016/j.nlm.2016.08.010.

37. Saugstad, J. A., and Ingram, S. L. (2008) Group I Metabotropic glutamate receptors (mGlu1 and mGlu5), in *The Glutamate Receptors*, Humana Press, pp. 387-463.

38. Niswender, C. M., and Conn, P. J. (2010) Metabotropic glutamate receptors: physiology, pharmacology, and disease, *Annu. Rev. Pharmacol. Toxicol.*, **50**, 295-322, doi: 10.1146/annurev.pharmtox.011008.145533.

39. Mao, L. M., Yang, L., Tang, Q. S., Samdani, S., Zhang, G. C., and Wang, J. Q. (2005) The scaffold protein homer1b/c links metabotopic glutamate receptor 5 to extracellular signal-regulated protein kinase cascades in neurons, *J. Neuroscience*, **25**, 2741-2752, doi: 10.1523/JNEUROSCI.4360-04.2005.

40. Baudry, M., Greget, R., Pernot, F., Bouteiller, J.-M., and Bi, X. (2012) Roles of group I metabotropic glutamate receptors under physiological conditions and in neurodegeneration, *WIREs Membr. Transp. Signal.*, **1**, 523-532.

41. Holbro, N., Grunditz, Å., and Oertner, T. G. (2009) Differential distribution of endoplasmic reticulum controls metabotropic signaling and plasticity at hippocampal synapses, *Proc. Natl. Acad. Sci. USA*, **106**, 15055-15060, doi: 10.1073/pnas.0905110106.

42. Hayashi, M. K., Tang, C. Y., Verpelli, C., Narayanan, R., Stearns, M. H., et al. (2009) The postsynaptic density proteins shank and homer form a polymeric network structure, *Cell*, **137**, 159-171, doi: 10.1016/j.cell.2009.01.050.

43. Tu, J. C., Xiao, B., Naisbitt, S., Yuan, J. P., Petralia, R. S., et al. (1999) Coupling of mGluR/Homer and PSD-95 complexes by the shank family of postsynaptic density proteins, *Neuron*, **23**, 583-592, doi: 10.1016/S0896-6273(00)80810-7.

44. Sala, C., Roussignol, G., Meldolesi, J., and Fagni, L. (2005) Key role of the postsynaptic density scaffold proteins shank and homer in the functional architecture of Ca²⁺ homeostasis at dendritic spines in hippocampal neurons, *J. Neuroscience*, **25**, 4587-4592, doi: 10.1523/JNEUROSCI.4822-04.2005.

45. Sala, C., Pièch, V., Wilson, N. R., Passafaro, M., Liu, G. S., and Sheng, M. (2001) Regulation of dendritic spine morphology and synaptic function by Shank and Homer, *Neuron*, **31**, 115-130, doi: 10.1016/S0896-6273(01)00339-7.

46. Sala, C., Futai, K., Yamamoto, K., Worley, P. F., Hayashi, Y., and Sheng, M. (2003) Inhibition of dendritic spine morphogenesis and synaptic transmission by activity-inducible protein homer1a, *J. Neuroscience*, **23**, 6327-6337.

47. Ango, F., Prézeau, L., Muller, T., Tu, J. C., Xiao, B., et al. (2001) Agonist-independent activation of metabotropic glutamate receptors by the intracellular protein Homer, *Nature*, **411**, 962-965, doi: 10.1038/35082096.

48. 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, doi: 10.1371/journal.pone.0009755.

49. Moutin, E., Raynau, F., Roger, J., Pellegrino, E., Homburger, V., et al. (2012) Dynamic remodeling of scaffold interactions in dendritic spines controls synaptic excitability, *J. Cell Biol.*, **198**, 251-263, doi: 10.1083/jcb.2011110101.

50. Cingolani, L. A., Vitale, C., and Dityatev, A. (2019) Intra- and extracellular pillars of a unifying framework for homeostatic plasticity: a crosstalk between metabotropic receptors and extracellular matrix, *Front. Cell. Neurosci.*, **13**, 513, doi: 10.3389/FnCNS.2019.00513.

51. Thomazeau, A., Bosch, M., Essayan-Perez, S., Barnes, S. A., De Jesus-Cortes, H., and Bear, M. F. (2020) Dissociation of functional and structural plasticity of dendritic spines during NMDAR and mGluR-dependent long-term synaptic depression in wild-type and fragile X model mice, *Mol. Psychiatry*, doi: 10.1038/s41380-020-0821-6.

52. Turrigiano, G. G., and Nelson, S. B. (2004) Homeostatic plasticity in the developing nervous system, *Nat. Rev. Neurosci.*, **5**, 97-107, doi: 10.1038/nrn1327.

53. Celikel, T., Marx, V., Freudenberg, F., Zivkovic, A., Resnik, E., et al. (2007) Select overexpression of Homer1a in dorsal hippocampus impairs spatial working memory, *Front. Neurosci.*, **1**, 97-110, doi: 10.3389/neuro.01.1.1.007.2007.

54. Rozov, A., Zivkovic, A. R., and Schwarz, M. K. (2012) Homer1 gene products orchestrate Ca(2+)-permeable AMPA receptor distribution and LTP expression, *Front. Synap. Neurosci.*, **4**, 0, doi: 10.3389/fnsyn.2012.00004.

55. Hennou, S., Kato, A., Schneider, E. M., Lundstrom, K., Gähwiler, B. H., et al. (2003) Homer1a/Vesl-15 enhances hippocampal synaptic transmission, *Eur. J. Neurosci.*, **18**, 811-819, doi: 10.1046/j.1460-9586.2003.02812.x.

56. Holz, A., Mülsch, F., Schwarz, M. K., Hollmann, M., Dobroisy, M. D., et al. (2019) Enhanced mGlu5 signaling in excitatory neurons promotes rapid antidepressant effects via AMPA receptor activation, *Neuron*, **104**, 338-352, doi: 10.1016/j.neuron.2019.07.011.
ences brain structure and function, lithium effects on white matter, and antidepressant response in bipolar disorder: a multimodal genetic imaging study, *Prog. Neuro Psychoph*, 81, 88-95, doi: 10.1016/j.pnpb.2017.10.011.

83. Wells, T. T., Judah, M. R., Ellis, A. J., McGeeary, J. E., and Beever, C. G. (2015) Inhibition of attention for affective material: contributions by HOMER1 gene variation, *Psychol. Neurosci.*, 8, 495-508, doi: 10.1037/pne0000027.

84. Antontseva, E., Bondar, N., Reshetnikov, V., and Merkulova, T. (2020) The effects of chronic stress on brain myelination in humans and in various rodent models, *Neuroscience*, 441, 226-238, doi: 10.1016/j.neuroscience.2020.06.013.

85. Leber, S. L., Llenos, I. C., Miller, C. L., Dula, J. R., Haybaec, J., and Weis, S. (2017) Homer1a protein expression in schizophrenia, bipolar disorder, and major depression, *J. Neural Transm.*, 124, 1261-1273, doi: 10.1007/s00702-017-1776-x.

86. Bernard, R., Kerman, I. A., Thompson, R. C., Jones, E. G., Bunney, W. E., et al. (2011) Altered expression of Homer1b/C improves neuronal survival after traumatic neuronal injury, *J. Neurosci.*, 31, 16464-16472, doi: 10.1523/Jneurosci.1542-11.2011.

87. Conti, B., Maier, R., Barr, A. M., Morale, M. C., Lu, X., et al. (2007) Region-specific transcriptional changes following the three antidepressant treatments electro convulsive therapy, sleep deprivation and fluoroxetine, *Mol. Psychiatry*, 12, 167-189, doi: 10.1038/sj.mp.4001897.

88. Szumlinski, K. K., Lominac, K. D., Klescen, M. J., Oleson, E. B., Dehoff, M. H., et al. (2005) Behavioral and neurochemical phenotyping of Homer1 mutant mice: possible relevance to schizophrenia, *Genes Brain Behav.*, 4, 273-288, doi: 10.1111/j.1601-183X.2005.00120.x.

89. Lominac, K. D., Oleson, E. B., Pava, M., Klugmann, M., Schwarz, M. K., et al. (2005) Distinct roles for different Homer1 isoforms in behaviors and associated prefrontal cortex function, *J. Neurosci.*, 25, 11586-11594, doi: 10.1523/Jneurosci.3764-05.2005.

90. Serchov, T., Schwarz, I., Theiss, A., Sun, L., Holz, A., et al. (2020) Enhanced adenosine A1 receptor and Homer1 expression in hippocampus modulates the resilience to stress-induced depression-like behavior, *Neuropharmacology*, 162, 107834, doi: 10.1016/j.neuropharm.2019.107834.

91. Albert, P. R. (2019) Targeting Homer1 for rapid antidepressant effects, *Neuron*, 104, 182-183, doi: 10.1016/j.neuron.2019.10.003.

92. Treccani, G., Musazzi, L., Perego, C., Milanese, M., Nava, N., et al. (2014) Stress and corticosterone increase the readily releasable pool of glutamate vesicles in synaptic terminals of prefrontal and frontal cortex, *Mol. Psychiatry*, 19, 433-443, doi: 10.1038/mp.2014.5.

93. Musazzi, L., Torne, P., Sala, N., and Popoli, M. (2017) Acute stress is not acute: sustained enhancement of glutamate release after acute stress involves readily releasable pool size and synapsin I activation, *Mol. Psychiatry*, 22, 1226-1227, doi: 10.1038/mp.2016.175.

94. Popoli, M., Yan, Z., McEwen, B. S., and Sanacora, G. (2012) The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission, *Nat. Rev. Neurosci.*, 13, 22-37, doi: 10.1038/nrn3138.

95. Joëls, M., and Baram, T. Z. (2009) The neuro-symphony of stress, *Nat. Rev. Neurosci.*, 10, 459-466, doi: 10.1038/nrn2632.

96. 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, doi: 10.1016/j.neuroscience.2007.09.081.

97. Wang, Y., Rao, W., Zhang, C., Zhang, C., Liu, M. D., et al. (2015) Scaffolding protein Homer1a protects against NMDA-induced neuronal injury, *Cell Death Dis.*, 6, e1843, doi: 10.1038/cddis.2015.216.

98. Wang, Y., Zhao, M. M., Shang, L., Zhang, Y. G., Huang, C. G., et al. (2020) Homer1a protects against neuronal injury via PI3K/AKT/mTOR signaling pathway, *Int. J. Neurosci.*, 130, 621-630, doi: 10.1080/00207454.2019.1702535.

99. Fei, F., Rao, W., Zhang, L., Chen, B. G., Li, J., et al. (2014) Downregulation of Homer1b/C improves neuronal survival after traumatic neuronal injury, *Neuroscience*, 267, 187-194, doi: 10.1016/j.neuroscience.2014.02.037.

100. Diering, G. H., Nirujogi, R. S., Roth, R. H., Worley, P. F., Pandey, A., and Huganir, R. L. (2017) Homer1a drives homeostatic scaling-down of excitatory synapses during sleep, *Science*, 355, 511-515, doi: 10.1126/science.aai8355.

101. Chen, F. H., Polsinelli, B., Nava, N., Treccani, G., Elving, B., et al. (2020) Structural plasticity and molecular markers in hippocampus of male rats after acute stress, *Neuroscience*, 438, 100-115, doi: 10.1016/j.neuroscience.2020.05.001.