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Homers regulate drug-induced neuroplasticity: Implications for addiction

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ARTICLE INFO

Article history:
Received 9 May 2007
Accepted 23 July 2007

Keywords:
Homer proteins
Addiction
Glutamate
Nucleus accumbens
Prefronal cortex
Prenatal stress

ABSTRACT

Drug addiction is a chronic, relapsing disorder, characterized by an uncontrollable motivation to seek and use drugs. Converging clinical and preclinical observations implicate pathologies within the corticolimbic glutamate system in the genetic predisposition to, and the development of, an addicted phenotype. Such observations pose cellular factors regulating glutamate transmission as likely molecular candidates in the etiology of addiction. Members of the Homer family of proteins regulate signal transduction through, and the trafficking of, glutamate receptors, as well as maintain and regulate extracellular glutamate levels in corticolimbic brain regions. This review summarizes the existing data implicating the Homer family of protein in acute behavioral and neurochemical sensitivity to drugs of abuse, the development of drug-induced neuroplasticity, as well as other behavioral and cognitive pathologies associated with an addicted state.

1. Introduction

The hypothesis that abnormal corticolimbic glutamate transmission contributes to the pathophysiology of addiction emerged from decades of neurological, brain imaging, pharmacological, genetic and biochemical research in affected individuals, as well as behavioral, molecular, electrophysiological and neurochemical data derived from preclinical animal models of addiction [cf., 1–4]. The vast number of clinical neuroimaging studies conducted on addicted individuals reveal striking abnormalities in prefrontal cortex (PFC) activity, relative to control subjects, that include reduced basal metabolic activity, reduced regional activation upon presentation of cues associated with non-drug primary reinforcers and enhanced metabolic activity upon presentation of drug-associated cues [e.g., 5–9]. Importantly, these abnormalities in PFC activity appear to be common across various drug addictions (incl. cocaine, methamphetamine, alcohol, cannabis, heroin and dissociative anesthetics), as well as across such non-drug addictions as gambling, and correlate with self-reports of "craving" and impairments in self-control in addicted individuals [6,9–17].

Preclinical efforts to understand the cellular basis for drug addiction-related abnormalities in mesocorticolimbic glutamate function have employed a variety of experimental approaches to examine the psychobiological consequences of repeated, non-contingent drug administration [18–22] and many of these findings have been confirmed in various animal models of drug-taking or drug-seeking [cf., 23–27]. The integrity of the corticoaccumbens glutamate pathway is

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Abbreviations: AAV, adeno associated viral vector; CCHomer, coiled coil Homer; IEG, immediate early gene; KO, knock-out; mGluR, metabotropic glutamate receptor; NAC, nucleus accumbens; NMDA, *N*-methyl-D-aspartate; PFC, prefrontal cortex; PSD, postsynpatic density; VTA, ventral tegmental area; WT, wild type.

0006-2952/$ – see front matter
doi:10.1016/j.bcp.2007.07.031

required for expressing many drug-induced changes in behavior, including the sensitization of a drug's psychomotor-activating effects [e.g., 28–37], the development of tolerance to a drug's psychomotor-inhibiting effects [e.g., 38,39], drug-conditioned place-preference [e.g., 36,38,40–43], the maintenance of drug self-administration [e.g., 44–46] and the reinstatement of drug-seeking [47–56]. Further, *in vivo* microdialysis studies have revealed pronounced effects of either acute or repeated drug-induced changes in NAC or PFC extracellular levels of glutamate by a number of drugs of abuse, including: cocaine [e.g., 31,35,37,47,53,57,58], amphetamines [e.g., 20,59,60–62, but see 63], alcohol [38,39,64], nicotine [65–68] and opiates [69,70], implicating drug-induced changes in presynaptic aspects of corticoaccumbens glutamate transmission in mediating the changes in behavior produced by drugs of abuse. Finally, postsynaptic aspects of corticoaccumbens glutamatergic signaling regulate either the self-administration of various drugs of abuse, or the potential to relapse to drug-seeking, in both humans and laboratory animals. Acamprosate, a mixed antagonist at the NMDA ionotropic glutamate receptor (iGluR) and the mGluR5 subtype of the Group1 metabotropic glutamate receptor (mGluR) [71,72], is clinically effective at treating alcoholism [73,74] and may prove to be effective for treating psychomotor stimulant and opiate addiction [75,76]. Moreover, direct pharmacological manipulation of glutamate receptors within the PFC or the NAC result in reduced behavioral responsiveness to various drugs of abuse, including cocaine [48,50,53,77–79; but see 80], alcohol [e.g., 44,81,82], amphetamines [e.g., 83–89] and opiates [40,90,91, but see 79], and systemic administration of antagonists of glutamate receptors blocks several aspects of nicotine reward in laboratory animals [e.g., 92–99, but see 100]. Taken together, these data pose cellular factors regulating pre- and postsynaptic aspects of corticoaccumbens glutamatergic transmission as likely molecular candidates contributing to an addicted phenotype. This review summarizes the evidence supporting a key role for the Homer family of proteins in corticoaccumbens glutamate transmission as it relates to the psychomotor-activating and rewarding properties of drugs of abuse.

2. Molecular aspects of Homer proteins

The Homer family of proteins is the product of three independent mammalian genes (*Homer1–3*), one *Xenopus* gene and one *Drosophila* gene [101–104]. In humans, Homer1, Homer2 and Homer3 are localized to chromosomes 5, 15 and 19, respectively [104] and Homer transcripts have been identified in many different tissues including: brain, retina, liver, kidney, spleen, testis, thymus, placenta, intestine, as well as cardiac, skeletal and smooth muscle [104–106]. First described in the late 1990s, the original family of Homer proteins consisted of Homer1a/b/c, Homer2a/b and 3 [101–104]. Since that time, 21 *Homer* mRNAs have been isolated from rat, mouse and human brain, however the proteins for some of these mRNAs have yet to be detected in mammalian brain tissue [106–108]. The mammalian genes encoding the Homer family of proteins have open reading frames that spread over 10 exons and can give rise to both constitutively expressed, as well as immediate early gene (IEG) products [101,103,109,110]. Exon 1 encodes the 5′ untranslated region (UTR) and contains the translational initiation codon ATG. Upstream of the initiation condon lie several multiple start site elements downstream motifs [MED-1; GCTCC(G/C)] indicating that *Homer* genes may contain multiple transcription initiation sites. Also located up-stream of the putative start site is a number of transcription factor binding sites, including: Sp1 (specific promoter 1), AP1 (activator protein 1), GATA, octamer recognition site, E box (enhancer box element) and CRE (cyclic adenosine monophosphate response element) [e.g., 109]. Thus, the transcription of *Homer* genes can be influenced by activation of immediate early genes and the mitogen-activated protein kinase (MAPK) cascade, as well as by CRE binding protein (CREB), all of which are highly implicated in the neurobiology of addiction [cf.,111–117].

With the exception of the recently characterized Homer1g [110], exons 2–5 encode an Enabled/vasodilator-stimulated phosphoprotein (Vasp) homology 1 (EVH1) domain [118,119], which is similar in sequence to other Ena/Vasp proteins that regulate cytoskeleton dynamics [120]. The EVH1 domain exhibits a RxxxxxGLGF sequence that is common to most post-synaptic density 95(PSD-95)/*Drosophila* discs large tumor suppressor gene (Dlg)/Zona occludens-1 (ZO-1) (PDZ) domains that mediate protein–protein interactions and are involved in ion channel and receptor targeting to the plasma membrane [cf., 121]. The EVH1 domain exhibits a high degree of similarity across Homer isoforms and is essential for Homer interactions with a proline-rich sequence (PPSPF) displayed by proteins regulating drug-induced alterations in neuronal morphology, synaptic architecture, and glutamate receptor signaling/intracellular calcium dynamics. Of particular relevance to drug-induced neuroplasticity [e.g., 20,73,74,78–82,89,40,90–99,122–129], these proteins include the mGluR1a and mGluR5 subtypes of Group 1 metabotropic glutamate receptors (mGluRs) [34,101,103,106,130–136], the NMDA glutamate receptor scaffolding protein Shank [38,131,137,138], the inositol-1,4,5-triphosphate (IP3) receptor, a down-stream mediator of Group1 mGluR signaling [132,139–143], F-actin [144–150], and phosophoinositide 3 kinase (PI3K) enhancer-long (PIKE-L) [151] (see Fig. 1).

In contrast to the high (~80%) sequence homology within exons 2–5 of the 3 *Homer* genes, exons 6–10 exhibit low homology (~20–30%) [104,106]. Exons 6–10 encode the carboxy-tail of the majority of Homer proteins that consists of a coiled-coil (CC) domain, 2 leucine zipper motifs and encode also the 3′ UTR [103,104,106]. Homer proteins multimerize through CC/leucine zipper motif interactions [103,104,106,132,142,143] and a recent elucidation of the quaternary structure of Homers indicate that these proteins form tetramers with each monomer oriented in parallel [142]. The tetrameric structure of Homer oligomers confers slower turn-over rates and greater efficiency of localization to dendritic spines [142].

Alternative transcript splicing in regions downstream from exon 5 has been reported for all 3 *Homer* genes and can result in premature termination of transcription prior to the sequences encoding the CC and leucine zipper motifs [101,104,106,109]. This premature termination of transcription results in truncated or ''short'' Homer isoforms that lack the motifs necessary to multimerize. In neurons, the most characterized

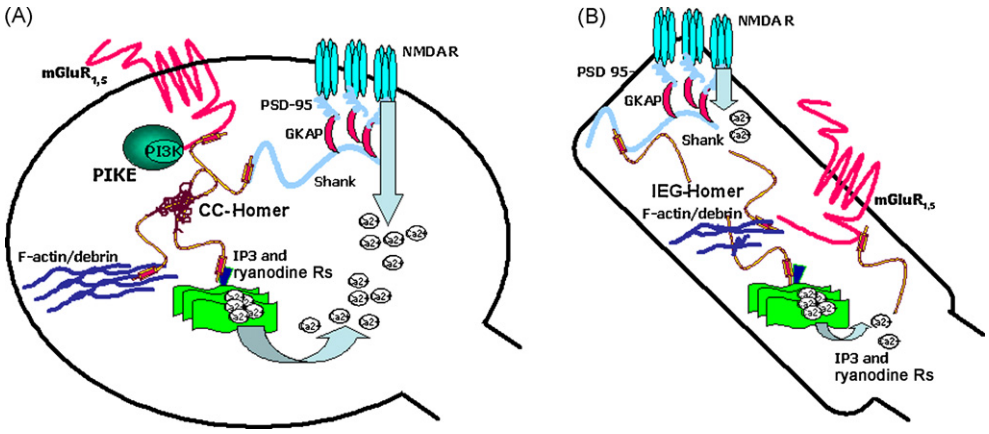

Fig. 1 – Illustration of the putative interactions between (A) constitutively expressed (CC) Homer proteins and (B) IEG Homer proteins with their EVH1-bound partners within the postsynaptic density of dendritic spines.

and thoroughly investigated is the bimodal expression of Homer1 constitutive (Homer1b-g) and IEG (Homer1a and Ania-3) products [cf.,144–148]. Within the *Homer1* gene lies transcriptional stop codons in intron 5 and sequence comparison between rat cDNA for *Homer1a* [101,149] and the mouse *Homer1* gene established that *Homer1a* mRNA terminates ~4.4 kb into intron 5 [109]. The intronic sequence extends exon 5 by 33 bases (11 codons), followed by a translational stop codon, and a ~4.4 kb 3′ UTR, colinear with the 5′ portion of intron 5. Ania-3, the other known IEG Homer1 isoform [107], is generated by alternative transcript splicing from exon 5 into an intron 5 sequence that lies ~5.7 kb downstream of the poly adenylation (polyA) site for *Homer1a* mRNA [109]. The precise sequence contribution to the premature transcript termination for *Homer1a* and *Ania-3* is not known. Examination of the 30 kb intron 5 sequence of *Homer1* failed to reveal obvious contributing sequences and no conserved sequences have been reported 5′ or 3′ of the poly(A) sites for these IEG transcripts. Moreover, the human intron 5 of *Homer1* did not provide any indication of highly conserved sequence islands that might function in the activity-dependent termination of transcripts within this intron [109]. However, the mRNA for IEG *Homer1* isoforms does contain several AUUUA repeats at their 3′ UTRs that may be responsible for destabilizing interactions with ribosomal translational machinery. While not involved in premature termination of transcription, this sequence likely contributes to the characteristic IEG-like, fast decay of mRNA transduction exhibited by *Homer1a* and *Ania-3* [109].

3. Homers are regulated within addiction-related neural circuits by drugs of abuse

With the exception of the inducible, IEG, Homer1 isoforms, CC-Homer proteins are expressed in similar quantities in brain, but differ somewhat in their regional distribution [104–106,143]. Relevant to addiction, Homer transcripts or proteins are present in many of the structures within mesocorticolimbic circuits that exhibit pathology in addiction [cf., 2,4,23,53,150–155]. CC-Homer and IEG Homer isoforms are found throughout the cerebral cortex [104,105]. Homers appear to be differentially distributed within hippocampus; Homer1b/c is localized to the CA1, CA2, CA3, dentate gyrus and subiculum, where Homer3a/b labeling is high in CA3, but intermediate in CA2 regions, respectively [105]. In contrast to CC-Homer1 isoforms, the induction of Homer1a reveals mRNA expression within the CA1, CA2 and CA3 regions, but not in the dentate gyrus [143]. Homer2a/b labeling is intense in CA1 and CA2, with intermediate labeling in the subiculum [105]. All three Homer isoforms, including the inducible forms, are located within the dorsal and ventral aspects of the striatum [104,105,143], and in the amygdala [156], but only Homer1 and Homer2 isoforms have been localized within thalamus [104,105]. In addition to these limbo-corticostriatal structures, all three Homer isoforms are located within cerebellum [105] and while the expression of Homer3 within the olfactory bulbs is developmentally down-regulated, the expression of both Homer1 and Homer2 isoforms persist throughout development [105]. Within neurons, Homer proteins are localized predominantly in the soma and apical dendrites [101,104,143,157]. At a subcellular level, Homer proteins are enriched within the postsynaptic density (PSD) fraction, but are also present in the crude nuclear, synaptosomal and microsomal fractions [104,143]. Homer2 differs from the other Homer isoforms as it is also localized to the soluble fraction and the synaptic vesicle fraction [104], implicating these isoforms in drug-induced changes in vesicular trafficking of receptor proteins.

First characterized as a gene whose mRNA expression is up-regulated within 1–3 h following the application of supra-physiological electrical stimulation of the hippocampus [101,103,149], an up-regulation in either *Homer1a* and/or *Ania-3* mRNA expression occurs within various cortical and limbic structures following various experimental manipulations relevant to drug addiction, including exposure to pharmacological and environmental stressors, as well as following the administration of a variety of drugs of abuse (see Table 1) [cf., 144,145]. *Homer1a* or *Ania-3* mRNA expression is increased within PFC and/or NAC upon acute injection of psychomotor stimulants [101,158–159], the hallucinogen LSD

Table 1 – Summary of findings regarding the regulation of IEG Homer expression *in vivo* by drugs of abuse (Rx = treatment)

Homer isoform	Region	Treatment	Effect vs. control	Reference
Acute drug treatment				
Homer1a	Striatum	Cocaine injection	mRNA ↑ at 2 h protein ↑ at 2 h	[101] [165]
	NAC	Cocaine injection	mRNA ↑ at 2 h	[159]
	Neocortex or PFC	Cocaine injection	mRNA ↑ at 1–2 h	[158,159]
	VTA	Cocaine injection	mRNA ↑ at 2 h	[159]
	Neocortex	Methamphetamine injection	mRNA ↑ at 1 h	[158]
	PFC, auditory and granular retrosplenial cortices	Phencyclidine (PCP) injection	mRNA ↑ at 2 and 24 h	[163]
	PFC	Lysergic acid diethylamide (LSD) injection	mRNA ↑ at 1.5 h	[160]
Ania-3	PFC	LSD injection	mRNA ↑ at 1.5–3 h	[160,161]
Repeated drug treatment				
Homer1a	PFC, NAC, and VTA	Cocaine injections	no change	[159]
	Neocortex	Methamphetamine injections + methamphetamine or cocaine challenge injection	mRNA ↑ at 1 h	[158]
	NAC	Nicotine injections	mRNA ↓ after 3 days of Rx no change after 7 or 14 days of Rx	[162]
Ania-3	frontal cortex	Morphine injections + withdrawal with or without a naloxone injection	mRNA ↑ at 4 h	[164]

[160,161], nicotine [162], and the dissociative anesthetic phencyclidine [163]. While the repeated administration of cocaine or nicotine induces a tolerance in the capacity of the drug to elevate NAC *Homer1a* levels [159,162], the capacity of methamphetamine to elevate mRNA levels persists within PFC with repeated drug treatment [158]. Similarly, *Ania-3* mRNA is up-regulated within frontal cortex by morphine in dependent animals, and this effect is observed also following naloxone-precipitated withdrawal [164]. A recent report by Zhang and colleagues [165] extended earlier data for cocaine-induced changes in *Homer1a* mRNA by demonstrating a transient (2–12 h), dose-dependent increase in Homer1a protein within both the dorsal and ventral aspects of the striatum following acute drug administration (see Table 2). Consistent with these data, immunoblotting studies in our laboratory have failed to detect changes in Homer1a levels within the PFC, NAC, dorsal striatum or hippocampus of either rats or mice at 3 weeks withdrawal from repeated cocaine injections (Table 2) [227]. Thus, while many drugs of abuse increase corticoaccumbens IEG Homer expression, this drug effect is transient and independent of a particular mechanism of drug action. In contrast to IEG Homers, the regulation of corticoaccumbens CC-Homer expression by drugs of abuse is more complex (Table 2) [39,156,165–169] and, as will be discussed below in greater detail, may reflect a compensatory response to either the immediate or longer-term effects of drug administration upon corticoaccumbens glutamate transmission.

4. Homer regulation of corticoaccumbens glutamate *in vivo*

Originally hypothesized to serve as a protein scaffold that facilitated intracellular signaling through Group1 mGluRs and calcium-related interactions between these receptors and ionotropic NMDA receptors [e.g., 101,103,132,138], it is now clear that Homer proteins function to regulate many aspects of the functional architecture of glutamatergic synapses. As discussed above, Homers interact via their EVH1 domains with a wide variety of proteins and thus, function not only to scaffold receptors and ion channels on the plasma membrane to the cytoskeleton and intracellular signaling complexes, but also to regulate the function of plasma membrane ion channels and intracellular messenger systems that impact cellular signaling and cell excitability [cf., 144–148]. Moreover, Homer protein interactions with other cytosolic scaffolding proteins, in particular Shank, are necessary for morphological aspects of glutamate synapses [144,170; see below]. Despite a decade of *in vitro* studies, our understanding of the role for Homer proteins in regulating neurotransmission *in vivo* is limited to phenotypic studies of *Homer* transgenic and null mutant mice (see Table 3). Nevertheless, the *in vivo* data are consistent with an important role for the Homer family of proteins in regulating the synaptic architecture and physiology of glutamate neurons in brain [cf., 144–146,148], which are theorized to be involved in regulating addiction vulnerability [147].

Homer knock-out (KO) mice exhibit a number of abnormalities in corticofugal glutamate transmission, some of which depend upon the deleted gene. Both *Homer1* and *Homer2* KO mice exhibit an approximately 50% reduction in NAC basal extracellular levels of glutamate [34,38,171]. Importantly, restoration of NAC Homer2 levels via the local infusion of an adeno-associated viral vector (AAV) carrying *Homer2b* cDNA normalizes glutamate levels in *Homer2* KO mice, supporting an active role for this CC-Homer isoform in regulating basal NAC glutamate content [34,38]. Interestingly, *Homer2* deletion does not affect basal glutamate content within the PFC, while *Homer1* deletion elevates PFC glutamate

Table 2 – Summary of findings regarding the regulation of CC-Homer protein or mRNA expression *in vivo* by drugs of abuse (Rx = treatment)

Homer isoform	Region	Treatment	Effect	Reference
Acute drug treatment				
Homer1b/c	NAC	Cocaine injection	Protein ↑ at 1 h	[326]
	NAC	Alcohol injection	No change in protein at 24 h	[254]
	Cerebellum	Cocaine injection	Protein ↑ at 15 h	[238]
Homer2a/b	NAC	Alcohol injection	Protein ↑ at 24 h	[254]
Homer3a/b	Cerebellum	Cocaine injection	Protein ↑ at 15 h	[238]
Repeated drug treatment				
Homer1b/c	NAC	Cocaine injections	No change in protein at 24 h Protein ↓ at 3 weeks	[168,227]; Fig. 1
	NACcore	One-hour cocaine self-administration	Protein ↓ at 24 h, but not at 2 weeks	[236]
		Six-hour cocaine self-administration	Protein ↓ at 24 h, but not at 2 weeks	[236]
	NAC	Methamphetamine injections	No change at 24 h Protein ↑ at 3 weeks	[285]
		Alcohol injections	No change at 24 h	[254]
		Continuous alcohol consumption	No change at 2 days, 2 weeks and 2 months	[39]
		Binge alcohol consumption	No change at 24 h	[255]
		Nicotine injections	mRNA ↑ after 14, but not 3 or 7 days Rx	[162]
	Amygdala	Nicotine injections	Protein ↑ after 3, but not 7 or 14 days Rx; no mRNA change with any Rx	[162]
	VTA	Nicotine injections	Protein ↑ after 3, but not 7 or 14 days of Rx; no mRNA change with any Rx	[162]
	PFC	Cocaine injections	No protein change at 24 h or 3 weeks	[168,227]; Fig. 1
		One-hour cocaine self-administration	No change in protein at 24 h or 2 weeks	[166]
		Six-hour cocaine self-administration	Protein ↑ at 24 h, but not at 2 weeks	[166,236]
	Cerebellum	Cocaine injections	Protein ↑ at 15 h	[238]
Homer2a/b	NAC	Cocaine injections	Protein ↓ at 3 weeks	[227]; Fig. 1
	NACcore	One-hour cocaine self-administration	No change at 24 h Protein ↓ at 2 weeks	[236]
		Six-hour cocaine self-administration	No change at 24 h Protein ↓ at 2 weeks	[236]
	NAC	Methamphetamine injections	No change at 24 h Protein ↑ at 3 weeks	[285]
		Alcohol injections	Protein ↑ at 24 h	[254]
		Continuous alcohol consumption	Protein ↑ at 2 days, 2 weeks and 2 months	[39]
		Binge alcohol consumption	Protein ↑ at 24 h	[255]
		Nicotine injections	No change in mRNA or protein	[162]
	Amygdala	Nicotine injections	mRNA ↑ after 3, but not 7 or 14 days Rx no protein change with any Rx	[162]
	VTA	Nicotine injections	Protein ↑ after 3, but not 7 or 14 days of Rx no mRNA change with any Rx	[162]
	PFC	Cocaine injections	Protein ↑ at 3 weeks	[227]; Fig. 1
		One-hour cocaine self-administration	No change in protein at 24 h or 2 weeks	[168]
		Six-hour cocaine self-administration	No change in protein at 24 h or 2 weeks	[168]
Homer3a/b	Cerebellum	Cocaine injections	Protein ↑ at 15 h	[238]

content by approximately 50% [34,171,172]. AAV-mediated transfection of PFC neurons with *Homer1c* cDNA, but not *Homer1a* cDNA, restored PFC basal glutamate levels to wild-type (WT) controls, implicating CC-Homer1 isoforms in regulating extracellular glutamate levels within this region [172]. At the present time, it is not entirely clear how deletion of *Homer* genes lead to such pronounced changes in basal glutamate content within the corticoaccumbens pathway. NAC extracellular glutamate levels are regulated primarily through a sodium-independent cystine-glutamate anti-porter, system Xc [173]. *Homer2* deletion attenuates NAC cystine-glutamate anti-porter function, a finding attributed to reduced protein expression of the Xc-catalytic subunit [34]. As the cystine-glutamate anti-porter does not contain the PPSPF necessary for Homer binding, it is likely that Homer regulation of anti-porter function is indirect. Stimulation of presynaptically localized mGluR1 receptors leads to elevations in extracellular glutamate levels within both the NAC and PFC [168,174]. While *Homer2* deletion reduces the total mGluR1 protein expression within the NAC and reduces agonist-stimulated glutamate release within this region [34], recent immunoblotting studies conducted on *Homer1* WT and KO mice have failed to detect genotypic differences in Group1 mGluR expression within any brain region examined (Table 3) [175]. Thus, the effects of *Homer1* deletion upon basal glutamate content can be dissociable from effects upon Group1 mGluR function/expression. Homers regulate the plasma membrane trafficking of NMDA receptors via interactions with a trimeric Shank–GKAP–PSD95 complex that binds to NR2 subunits of the NMDA receptor [137,138,150]. While

Table 3 – Comparison of the corticolimbic glutamate alterations produced by *Homer1* and *Homer2* deletion. ND = not yet determined

Region	Measure	*Homer1*	*Homer2*	Reference
NAC	Basal glutamate content	WT > KO	WT > KO	[34,38,171,172]
	Cocaine-induced glutamate release	WT < KO	WT < KO	[34,171,172]
	Alcohol-induced glutamate release	ND	WT > KO	[38]
	Group1 mGluR agonist-induced glutamate release	ND	WT > KO	[34]
	Cystine-induced glutamate release	ND	WT > KO	[34]
	Total mGluR1a protein	WT = KO	WT > KO	[34,175]
	Plasma membrane mGluR1a protein	ND	WT = KO	[38]
	Total mGluR5 protein	WT = KO	WT = KO	[34,175]
	Plasma membrane mGluR5 protein	ND	WT = KO	[38]
	Total NR2a	WT = KO	WT = KO	[34,175]
	Plasma membrane NR2a protein	ND	WT > KO	[38]
	Total NR2a	WT = KO	WT = KO	[34,175]
	Plasma membrane NR2a protein	ND	WT > KO	[38]
	Total Xc expression	ND	WT > KO	[34]
PFC	Basal glutamate content	WT < KO	WT = KO	[34,171,172]
	Cocaine-induced glutamate release	WT > KO	WT = KO	[171,172]
	High potassium-stimulated release	WT > KO	ND	[169]
	Total mGluR1a, mGluR5, NR2a, NR2b protein	WT = KO	ND	[175]

neither deletion of *Homer1* nor *Homer2* alters total NMDA receptor subunit expression within the NAC or PFC (Table 3) [34,175], *Homer2* deletion reduces the NAC plasma membrane expression of NR2a and NR2b NMDA receptor subunits *in vivo* [38]. Through the Shank–GKAP–PSD95 complex, NR2 subunits colocalize with nitric oxidase synthase-1 (NOS-1) [176–178], an enzyme responsible for the synthesis of the retrograde messenger nitric oxide (NO) [179,180]. Thus, one testable hypothesis to account for the effects of Homer deletion upon basal and stimulated corticoaccumbens glutamate transmission relates to alterations in NMDA-mediated NO retrograde signaling [181,182]. While the precise molecular mechanisms involved in Homer regulation of corticoaccumbens glutamate transmission remain elusive, it is clear from the phenotypic characterization of Homer mutant mice that this family of proteins is necessary for the normal regulation of corticoaccumbens glutamate transmission *in vivo*. The putative role for abnormalities in corticoaccumbens glutamate transmission in addiction (see above) render members of the Homer family of proteins likely molecular candidates in the pathophysiology of this disorder.

5. Potential role for Homers in drug-induced alterations in structural plasticity

Mounting evidence supports the theory that the addicted state results from a drug-induced usurpation of the cellular and molecular mechanisms underlying other forms of synaptic plasticity (e.g., learning and memory) within the neural circuits underlying motivation and psychomotor activation [cf., 183,184]. Moreover, the chronic nature of addiction suggests that drug-induced structural plasticity within these neural circuits endures for months, if not years, following cessation of drug administration [183,184]. Indeed there exists now considerable data supporting persistent effects of various drugs of abuse upon neuronal morphology, particularly in the structural plasticity of dendritic spines of neurons within the PFC and NAC. Dendritic spines are highly motile, tiny membrane protuberances that are the postsynaptic contact site for the vast majority (>90%) of excitatory synapses in the brain. One cardinal feature of dendritic spine is the postsynaptic density (PSD), an electron-dense fibrous structure, consisting of clusters of neurotransmitter receptors, receptor-associated scaffolding and signaling proteins, as well as high concentrations of cytoskeletal proteins that cross-link actin filaments with the plasma membrane, the PSD, and the smooth endoplasmic reticulum present in some spines [121,185–190]. Experience-dependent changes in spine shape, size and number contribute to alterations in synaptic strength, in part by regulating connective opportunities [191–193] and neuronal morphology, as well as the ability to induce morphological changes within dendritic spines depends upon an intact cytoskeleton [196]. Increases in spine size, emergence of new spines and the perforation of the PSD are all thought to reflect spine head splitting and synapse duplication, contributing to a long-lasting enhancement of synaptic efficacy [e.g., 191–196].

While the effects of repeated drug experience upon structural plasticity within the corticoaccumbens glutamate pathway have been examined for a number of drugs of abuse, the large majority of studies assessed the long-term consequences of repeated cocaine or amphetamine exposure upon dendritic morphology [for review, 183]. In all studies to date, both non-contingent and contingent cocaine or amphetamine administration were found to increase spine density, as well as dendritic branching on medium spiny GABAergic neurons within both the shell and core subregions of the NAC [197–206]. Similarly, repeated treatment with both psychomotor stimulants increase spine density and branching of the apical, and to a lesser extent the basalar, dendrites of glutamatergic pyramidal neurons within the PFC [197–200,203,204]. These structural data are consistent with greater levels of filamentous actin (F-actin) within the NAC following both acute exposure to and withdrawal from repeated cocaine exposure [128]. As observed for psychomotor stimulants, nicotine also increases spine density in both PFC and the shell subregion of the NAC [207,208]. The structural

changes induced by the above drugs are detectable at 24–48 h following discontinuation of chronic drug treatment [206] and can be observed for up 3.5 months [201,208]. Similar to nicotine and psychomotor stimulants, the structural plasticity associated with morphine treatment has been described a month after the last treatment [209,210]. However, the morphological changes induced by chronic morphine experience are very different from those induced by nicotine and stimulant drugs, characterized by marked decreases in spine density in both the shell of the NAC and medial PFC and decreased dendritic branching [209,210]. More well-characterized for hippocampus, chronic alcohol produces yet another distinct set of morphological changes within dendrites, compared to other drugs of abuse [211–214], characterized by increases in the ratio of wide and stubby spines to thin and mushroom-shaped spines [211–213]. A recent study of the effects of chronic alcohol consumption (14 weeks exposure) revealed a number of dendritic abnormalities within the NAC, including a decrease in spine density, a thickening of the spine head and a disturbance in spine orientation [214]. Moreover, a subpopulation of medium spiny neurons also exhibited multi-headed spines (bifurcates and triplicates emerging from a common neck) and stacked-head spines, which resembled beads on a string with one head growing out of the other in serial arrangement [214] – abnormalities observed also following repeated psychomotor stimulant drug administration [204]. In both the case of the NAC and hippocampus, the alcohol-induced increases in dendritic spine head size was accompanied by increased synaptic targeting of NMDA receptors and clustering with PSD-95, as well as an enlargement in PSD-95-associated F-actin clusters [213–215]. Taken together, these data support the hypothesis that chronic drug exposure engages homeostatic responses that alter the dendritic processing of glutamate, and other neurochemical signals, ultimately affecting synaptic efficacy within key brain regions regulating the addictive properties of drugs of abuse [122,183,184,215,216].

Homers are critical for regulating dendritic morphology and thus, these proteins are likely candidates involved in the morphological abnormalities produced by repeated drug experience. The co-transfection of Homer1b with Shank1b in developing hippocampal neuronal cultures induces the maturation of spines and causes an enlargement in dendritic spine size, compared to the transfection of either protein alone [139,144,171]. Moreover, co-transfection of Homer1b with Shank1b also recruits IP3Rs and endoplasmic cisternae to the PSD [139,171]. The maturation and enlargement of spines requires the physical interaction of Homer and Shank as co-transfection of Homer1b with a mutant form of Shank that is incapable of binding Homer or the co-transfection of Shank1b with the truncated Homer1a did not alter spine size or shape [139,171]. Within the PSD, CC-Homer proteins colocalize with F-actin/Shank/PSD-95/GKAP/NMDA receptor clusters [131,146]. Corresponding to the maturation and enlargement of dendritic spines by Homer–Shank interactions [e.g., 144] is the recruitment of the NR2b subunit of the NMDA receptor, as well as, a number of other scaffolding and signaling molecules associated with glutamate receptors, including GKAP, PSD-95, IP3Rs, F-actin and various proteins related to the endoplasmic reticulum cisterna [131,139,144–146,150,171]. In mature neurons, the distribution and clustering of CC-Homers within dendritic spines is regulated by neuronal activity. High potassium-stimulated neuronal depolarization and subsequent fast, transient calcium entry induces the translocation of CC-Homers to spines and a marked increase in the number of Homer–NMDA receptor punctae [217,219]. Moreover, calcium entry via voltage-gated calcium channels also stimulates CC-Homer–NMDA clustering [217]. In contrast, the application of glutamate and stimulation of calcium entry through NMDA receptors causes Homer de-clustering and reduces the amount of CC-Homer–NMDA punctae within the spine [217]. While activation of protein kinase C (PKC) does not affect the intracellular distribution of CC-Homers, it induces the recruitment of Homer1a from the soma to the dendritic spine [217], a process expected to weaken synaptic efficacy. Thus, the regulation of calcium influx, in particular the kinetics of calcium entry, appears to be an important determinant in the localization of Homers to the PSD.

The formation of Homer-containing multi-protein clusters is developmentally regulated [131,219]. In one study by Shiraishi et al. [131], image analysis of developing hippocampal neuronal cultures revealed the localization of Homer2/NR2B/PSD-95 clusters along the soma and proximal dendrites at 7 days *in vivo* (DIV) and these clusters migrated towards the dendritic head and developing spines by 21 DIV, where they co-localized with F-actin [131]. In another study, the size of Homer1c/PSD-95 clusters increased progressively between 11 and 17 DIV and newly formed dendrites rapidly accumulated Homer1c. The density of Homer1c/PSD-95 clusters can be enhanced by activation of the protein kinase cAMP-dependent kinase (PKA) [219], furthering the evidence that neuronal activity regulates the translocation of Homer proteins to dendritic spines. While not yet assessed in developing cortical neurons, both IEG and CC-Homers play a critical role in axonal pathfinding in optical tectal neurons [220]. Transfection of this neuronal type with Homer1a, Homer1c or a mutant of Homer1c that interferes with the EVH1-binding domain on interacting proteins induces aberrant axonal projections and irregular dendritic arborization, while transfection with a mutant for Homer1a that does not interact with the EVH1-binding domain on interacting proteins prevented alterations in neuronal morphology and the alterations in axonal trajectories. Thus, there appears to be an optimal level of functional CC-Homer required in the growth cone for normal axonal pathfinding [220] and it is tempting to speculate that early environmental insults might alter Homer expression and produce abnormalities in neuronal orientation, morphology and axonal connections, as reported in the brains animals exposed prenatally to drugs of abuse or stress [e.g., 184,221].

6. Homers and cocaine-induced neuroplasticity

Obligatory for the production and maintenance of many of the enduring neuroadaptations produced by exposure to cocaine, drug-induced abnormalities in corticoaccumbens glutamatergic projections produce the key behavioral characteristic of cocaine addiction [for reviews, 2,4,19,23,222]. As discussed above, repeated cocaine exposure elicits numerous alterations

in corticoaccumbens glutamatergic function that include alterations in NAC basal glutamate content [e.g., 47,34,35], a sensitized NAC and PFC glutamate response to a cocaine challenge injection [e.g., 31,32,35,37,52] and complex alterations in both the function and expression of iGluRs, mGluRs and glutamate transporters [for reviews, 2,4,18,20, 223–226]. As Homer isoforms regulate both pre- and postsynaptic aspects of glutamatergic signaling within this pathway [cf., 144–148], these proteins are likely molecular candidates mediating the cocaine-induced glutamatergic abnormalities contributing to the addictive and psychomotor-activating properties of this drug [147].

As presented in Table 1, the mRNA for IEG Homer1 isoforms is up-regulated within 1–3 h in brain following an acute cocaine injection [101,159,165]. In dorsal striatum, nucleus accumbens and frontal cortex, the elevation in Homer1a protein expression by an acute injection of cocaine resembles that of the IEG C-Fos, is dose-dependent and correlates with the magnitude of locomotor hyperactivity exhibited by rats [165]. By inhibiting plasma membrane transporters, cocaine prevents the re-uptake of dopamine, serotonin and norepinephrine and thus, enhances levels of these neurotransmitters within the synapse [227]. Pretreatment of animals with the selective D1 receptor antagonist SCH23390, but not the selective D2 receptor antagonist eticlopride, prevents the cocaine-induced rise in striatal Homer1a protein expression supporting a key role for D1 receptor signaling in mediating this effect [167]. Moreover, in striatal cultures, a dopamine-induced induction in Homer1a expression could be mimicked by the protein kinase A (PKA) activator 8-bromo-cAMP and attenuated by the PKA inhibitor H89, the calcium/calmodulin-dependent protein kinase (CaMK) inhibitor KN62 or anti-sense oligonucleotides against the transcriptional regulator CREB (cAMP response element binding protein) [167]. These data provided the first insight into the intracellular signaling cascade(s) involved in the regulation of *Homer1a* transcription and point to an important role for dopamine D1 receptor-mediated activation of CREB in this regard [167].

The cocaine-induced rise in *Homer1a* mRNA and protein expression is transient, dissipating within 6–12 h following cocaine injection [101,165] and shows tolerance with repeated cocaine administration [159]. However, cocaine-induced changes in addiction-related behavior, as well as, pre- and postsynaptic alterations in corticoaccumbens glutamate transmission are either absent or minimal during the first 1–3 days immediately following treatment, but are detectable after longer withdrawal periods [for reviews, 19,20,22]. Moreover, for certain cocaine-induced phenomena (e.g., motor hyper-activity, reinstatement of drug-seeking, accumbens glutamate sensitization), the drug effect can intensify with the passage of time and persist for months following the end of cocaine treatment [e.g., 19–21,113]. While the induction of striatal Homer1a expression may be involved in mediating the acute locomotor-activating properties of the drug, there exists no clear temporal relationship between cocaine's effects upon Homer1a expression and the manifestation of cocaine-induced neuroplasticity. However, consistent with earlier reports for the interactions between IEG and CC-Homer *in vivo* [144,146,148], the induction of Homer1a by cocaine disrupts CC-Homer–Group1 mGluR interactions as well as CC-Homer–IP3 receptor interactions *in vivo* [165]. This raises that possibility that the relatively short-lived elevation in Homer1a by acute cocaine may allow for a rearrangement of the architecture of glutamatergic synapses, thereby initiating or enabling drug-induced plasticity within brain regions embedded within neural circuitry of addiction.

In contrast to IEG Homer isoforms, delayed changes in CC-Homer expression are produced within limbic regions following repeated non-contingent cocaine administration that coincide with the manifestation of behavioral and neurochemical sensitization to this drug (see Table 2) [168,228]. Repeated injections of cocaine, followed by a 1–3-week period of withdrawal, augments the acute psychomotor-activating effects of the drug, a phenomenon referred to as behavioral sensitization [e.g., 19,20–22]. Immunoblotting conducted on tissue from Sprague Dawley rats indicated a coincident reduction in mGluR5 and Homer1b/c protein levels at 3 weeks withdrawal from repeated cocaine administration that was selective for the medial, but not the lateral, aspect of the NAC [168]. Identical cocaine treatment to C57BL/6J mice revealed a concomitant reduction in NAC levels of Homer1b/c and Homer2a/b, indicating that CC-products of both the *Homer1* and *Homer2* genes are similarly regulated within NAC by cocaine withdrawal (Fig. 2) [228]. As observed previously in the earlier rat study by Swanson et al. [168], PFC Homer1b/c levels were unchanged following withdrawal from repeated cocaine in mice; however, we observed an approximately 30% increase in PFC Homer2a/b expression (Fig. 2). Thus, repeated non-contingent, experimenter-administered cocaine elicits enduring, but opposite effects, upon Homer2a/b expression within the cell body and terminal regions of the corticoaccumbens glutamate pathway [228]. The regulation of mesolimbic Homer protein expression by cocaine has also been assessed in a ''long access'' animal model of addiction in which groups of animals are allowed to self-administer intravenous cocaine daily for either 1 h or 6 h [e.g., 229–231]. These two self-administration paradigms elicit very different patterns of cocaine intake (stable versus escalating, respectively) [e.g., 229] and result in very different neuroadaptations, as revealed by both behavioral and biochemical assays [229–236]. The effects of a history of cocaine self-administration upon corticoaccumbens CC-Homer expression are complex, dependent upon the duration of cocaine access, the duration of withdrawal and the region investigated (Table 2) [166,236]. As summarized in Table 2, the level of Homer1b/c, but not Homer1a, is reduced within the core subregion of the NAC at 24 h withdrawal from either 1-h or 6-h of cocaine self-administration and this effect dissipated by 2 weeks withdrawal. Short-term withdrawal from cocaine self-administration moderately reduced NAC Homer2a/b levels in both cocaine self-administering groups, but in contrast to Homer1b/c, this effect intensified with the passage of time (Table 2) [236]. In contrast to the selective effects of non-contingent cocaine injections upon PFC Homer2a/b expression [228], withdrawal from intravenous cocaine self-administration affected only PFC levels of Homer1b/c (Table 2) [166]. At 24 h withdrawal, an elevation in PFC Homer1b/c expression was observed in long-access animals but this effect was no longer apparent at 2 weeks withdrawal, whereas no change in PFC Homer1b/c levels was observed at 2 h withdrawal in short-

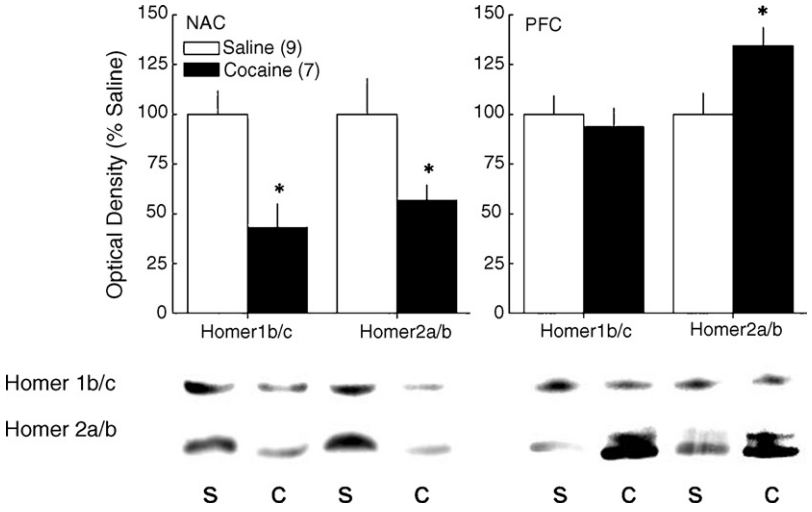

Fig. 2 – Homer protein levels are differentially regulated in the cell body and terminal regions of the corticoaccumbens glutamate pathway by cocaine. Immunoblotting for total Homer protein expression was conducted on NAC and PFC tissue from C57BL/6J mice at 3 weeks withdrawal from repeated cocaine (7 × 30 mg/kg) or saline administration. Bottom panels: Anti-Homer1b/c and anti-Homer2a/b primary antibodies recognized bands at 47 kDa [e.g., 39,143,168,294]. Left: Cocaine-treated mice showed an approximately 50% reduction in Homer1b/c (t_{20} = 2.34, p = 0.03) and Homer2a/b (t_{20} = 2.32, p = 0.03] within the NAC. *Right*: Cocaine-treated mice did not differ from saline controls regarding Homer1b/c expression (p = 0.95), but exhibited an approximately 30% increase in Homer2a/b (t_{20} = 2.45, p = 0.02). *p < 0.05 for saline vs. cocaine.

access animals but were significantly reduced at the 2-week time-point. It is clear that considerable work remains to understand the factors affecting and the mechanisms through which withdrawal from repeated cocaine experiences regulate the expression of CC-Homer isoforms in brain. However, as the changes in CC-Homer expression produced by withdrawal from repeated non-contingent or response-dependent cocaine administration are paralleled by changes in corticoaccumbens iGluR and mGluR expression/function [166,168,236], drug-induced alterations in glutamatergic signaling through Homer complexes may be important cellular adaptations to cocaine that contribute to the enduring consequences of repeated drug exposure upon brain and behavior.

Indeed, recent studies have established an important role for CC-Homer proteins in regulating sensitivity to the behavioral and neurochemical effects of cocaine. *Homer1* and *Homer2* KO mice exhibit enhanced cocaine-induced place-conditioning and cocaine-induced locomotor activity, and *Homer2* KO mice exhibit a shorter latency to acquire a lever-press response for intravenous cocaine, than do WT mice [34]. Similarly, a reduction in NAC Homer1b/c levels, produced by infusion of anti-sense oligonucleotides against *Homer1*, elicits a sensitized motor response in cocaine-naïve rats given an acute cocaine injection [237]. In cocaine-naïve *Homer1* and *Homer2* KO mice, the increases in behavioral sensitivity to cocaine are accompanied by a reduction in NAC glutamate content and an enhanced capacity of cocaine to elevate NAC glutamate levels [34,171]. Moreover, *Homer2* KO mice exhibit a reduction in the function and expression of both Group1 mGluRs and the cystine-glutamate transporter [34]. These behavioral and neurochemical alterations are akin to those observed in rodents with a history of repeated cocaine administration [e.g., 19,22,31,35,47,57,168], indicating that a reduction in CC-Homer1 and CC-Homer2 expression can elicit a ''pre-sensitized'' cocaine phenotype. In contrast to *Homer1* and *Homer2* gene products, Homer3 isoforms are localized primarily to hippocampus and cerebellum [104,105]. While both acute and repeated cocaine elevates cerebellar Homer3a/b expression [238], *Homer3* KO mice do not exhibit a cocaine ''presensitized'' behavioral phenotype [34]. While transgenic mice over-expressing Homer1a within striatal striosome patches exhibit increased locomotor sensitivity in response to an acute challenge injection of amphetamine [239], AAV-mediated over-expression of Homer1a within the NAC or PFC does not alter the acute or the sensitized locomotor response to cocaine [35,172]. However, AAV-mediated restoration of Homer2b to the NAC of *Homer2* KO mice reversed genotypic differences in cocaine-conditioned reward and motor activity [34] and either AAV- or TAT-mediated over-expression of Homer1c or Homer2b in the NAC of repeated cocaine-treated rats prevented the expression of cocaine-induced behavioral and glutamate sensitization when assessed at 3 weeks withdrawal from repeated cocaine exposure [35]. As repeated cocaine administration can produce a time-dependent down-regulation in CC-Homer1 and -Homer2 isoforms within the NAC (Fig. 1) [167,169,229,236], this collection of data for the NAC indicates cocaine-induced changes in CC-Homer1 and -Homer2 isoforms as important regulators of cocaine-induced neuroplasticity within this region.

Although withdrawal from repeated cocaine does not alter PFC basal glutamate content [47], it sensitizes the capacity of a challenge injection to elevate glutamate levels in this region [37]. Despite the pronounced abnormalities in NAC glutamate, *Homer2* KO mice do not exhibit alterations in basal or cocaine-stimulated glutamate release within the PFC [34]. In contrast, the cocaine ''pre-sensitized'' phenotype of *Homer1* KO mice is

accompanied also by an approximately 50% elevation in basal levels of glutamate and a blunting of the cocaine-induced rise in extracellular glutamate within the PFC [171]. Infusion of AAV-Homer1c to the PFC of *Homer1* KO mice reverses the elevated basal glutamate content, while infusion AAV-Homer1a had no effect [172]. Additionally, infusion of AAV-Homer1c, but not -Homer1a, reversed the genotypic difference in cocaine-induced elevations of glutamate in the PFC [172], indicating that cocaine-stimulated glutamate release within the PFC requires Homer1c. However, an intra-PFC infusion of AAV-Homer1a blunted the capacity of cocaine to elevate PFC glutamate in WT mice and reduced glutamate levels below baseline in KO animals, indicating an active and inhibitory role for this IEG isoform in cocaine-stimulated glutamate release [172]. Thus, cocaine-induced imbalances between IEG and CC-Homer expression may contribute to the enduring abnormalities in prefrontal cortex function observed in cocaine addicts and consistent with this notion, a single-nucleotide polymorphism on the first intron of *Homer1* (rs6871510) has been significantly associated with cocaine dependence in an African American population [240].

7. Homers and alcohol-induced neuroplasticity

Alcohol is a drug of abuse that inhibits iGluR and Group1 mGluR (mGluR5) receptor function [e.g., 241–243] and many of the acute behavioral effects of alcohol are related to the inhibition of glutamate receptor signaling within the meso-corticolimbic and extended amygdala circuits [for reviews, 122,126,152,215]. The dose–response function for acute alcohol-induced changes in corticoaccumbens extracellular glutamate is biphasic; lower doses either do not change or increase glutamate levels, while moderate to higher doses reduce glutamate levels [39,64,167,244]. Repeated alcohol administration alters basal glutamate content in the NAC [e.g., 38,245–247] and sensitizes the capacity of alcohol to elevate extracellular glutamate levels, at least within the NAC [38,39,248–250]. Moreover, repeated alcohol administration produces an enduring up-regulation in both iGluR and mGluR expression, function, as well as increased glutamate receptor trafficking to, and clustering within, the plasma membrane [39,122,212–215,251–253]. As these neuroadaptations are implicated in the development of alcohol dependence, tolerance, and addiction [122,126,147,152,213–215], recent immunoblotting studies examined the consequences of repeated alcohol exposure upon the protein expression of Homer isoforms within the NAC. Alcohol-experienced C57BL/6J mice revealed a pronounced (2.0–2.5-fold increase) and selective up-regulation in Homer2 protein expression within the NAC following various alcohol treatment regimens, including alcohol injection [254], chronic (3 months) continuous alcohol consumption [39] and repeated, binge alcohol intake [255] (Table 2). The capacity of alcohol to elevate NAC Homer2 levels is injection number-dependent, suggesting that this molecular adaptation is a direct pharmacological response to the drug [254]. Moreover, the approximately 2.5-fold increase in NAC Homer2 levels produced by a 3-month history of continuous alcohol drinking is very persistent and is unchanged at from 2 days to 2 months following the last drinking session [39]. Finally, under continuous and/or binge drinking conditions, the rise in Homer2 levels was accompanied by elevations in the total protein expression of Group1 mGluRs and NR2 subunits, as well as the activation of PI3K and PKCε [39,255], two down-stream intracellular mediators of Group1 mGluR signaling [141,256]. Thus, alcohol up-regulates the NAC expression of members of the mGluR–Homer–NMDA signaling complex and increases the activation of mGluR–Homer-mediated signaling cascades. Since alcohol is an antagonist at both NMDA and mGluR5 receptors [241–243], we propose that the observed up-regulation in glutamate receptor/Homer expression and kinase activation likely reflects a compensatory response to glutamate receptor blockade by alcohol. As chronic alcohol administration down-regulates ubiquitin-mediated degradation systems [e.g., 257,258], the persistence of alcohol's effects upon Homer and glutamate receptor expression might reflect decreased protein degradation, by virtue of alcohol's effect upon the ubiquitin system, Homer tetramerization, or both [39].

Neural and behavioral genetic studies support an important role for Homer proteins in regulating sensitivity to the behavioral and neurochemical effects of alcohol [38,39,259]. *Drosophila* Homer (D. Homer) is highly homologous to mammalian Homer1 proteins [260] and recent behavioral screens for *Drosophila* mutants revealed that *Drosophila* lacking *Homer* (*homer*^{R102}) exhibit increased sensitivity to the acute sedative effects of alcohol and fail to develop normal levels of rapid tolerance upon a subsequent alcohol exposure. In support of an active role for Homer in regulating alcohol sensitivity, pan-neuronal expression of WT Homer reduced their initial sensitivity to acute alcohol and restored the development of rapid tolerance [259]. These data for *Drosophila* are consistent with our earlier reports for altered alcohol sensitivity in mice lacking *Homer2* [38]. *Homer2* KO mice exhibit an alcohol-avoiding and -intolerant behavioral phenotype that is characterized by: alcohol-conditioned place-aversion, shifts to the right and down in the dose–response functions for alcohol preference and intake, increased alcohol-induced sedation and a lack of tolerance to the locomotor-inhibiting effects of alcohol upon repeated alcohol administration. While *Homer2* deletion does not alter the capacity of acute alcohol to affect NAC glutamate levels, KO mice fail to exhibit glutamate sensitization when treated repeatedly with alcohol [38]. AAV-mediated restoration of Homer2b to the NAC of *Homer2* KO mice completely reverses the alcohol behavioral and neurochemical phenotype of KO animals, supporting a link between alcohol reward and NAC glutamate sensitization [38]. Mimicking the effect of alcohol upon NAC Homer2 protein expression via AAV-mediated Homer2b over-expression in the NAC of WT mice on a C57BL/6J X 129sV/J genetic background enhances alcohol preference under free-access conditions in the home cage [38] and NAC over-expression of Homer2b in alcohol-preferring C57BL/6J mice facilitates the development of an alcohol-conditioned place-preference and shifts the alcohol-response functions for lever-pressing for alcohol, response-contingent alcohol consumption and alcohol preference in the home cage up and the left of control animals [38,39]. Moreover, NAC Homer2 over-expression in C57BL/6J mice facilitated the development of tolerance to the locomotor-impairing effects

of alcohol and augmented both the acute and sensitized glutamate response to alcohol [39]. Collectively, the immunoblotting and behavioral genetic studies to date implicate an up-regulation in NAC Homer2 expression as an important cellular adaptation to alcohol facilitating alcohol-induced changes in behavior, including alcohol drinking.

8. Homers and methamphetamine

Methamphetamine is the *N*-methylated analogue of amphetamine and is widely considered to be more potent and to have higher potential for addiction [261]. Like other amphetamines, methamphetamine increases extracellular levels of monoamines by disrupting vesicular storage and reversing the plasma membrane transporter [261–263]. While methamphetamine's effects upon the monoaminergic systems have received considerable experimental attention [for reviews, 263–269], less is known regarding the regulation of corticoaccumbens glutamate and glutamate receptor expression by amphetamine and methylated analogs. Acute administration of amphetamines is reported to produce either no change or a delayed rise in extracellular glutamate levels within striatal regions [59–62,270,271], while an acute injection of methamphetamine, but not amphetamine, elevates PFC glutamate levels [270]. Whereas repeated cocaine administration produces robust drug-induced glutamate sensitization within the NAC [e.g., 31,35,47,57], repeated dosing with non-toxic regimens of amphetamine or methamphetamine elicits little effect upon the capacity of these drugs to alter glutamate levels within the corticoaccumbens pathway [61,271]. In contrast, repeated high dose amphetamine or methamphetamine regimens that induce dopamine neurotoxicity produce an increase in glutamate content within the PFC [272], a delayed increase in dorsal and ventral striatal glutamate levels [60,273–276] and enhance potassium-stimulated, but not methamphetamine-stimulated, glutamate release within the PFC [276]. Whether or not the more modest effects of amphetamine regimens upon corticoaccumbens glutamate relate to the duration of withdrawal remains to be determined. In support of this possibility, reductions in the mRNA or protein expression of the AMPA receptor subunits GluR1 and GluR2, and the obligatory NMDA subunit NR1 within the NAC are observed at 14 days withdrawal, but not at earlier timepoints [277–280]. In contrast, changes in glutamate receptor subunit expression are apparent within the PFC during early withdrawal [277–281]. Of note, the amphetamine-induced changes in glutamate receptor subunit expression appear to be opposite to those reported previously for repeated cocaine [e.g., 282–284]. Thus, while cocaine and methamphetamine exert *qualitatively* similar effects upon extracellular monoamine levels [226,261,263], the enduring effects of these two psychomotor stimulants upon corticoaccumbens glutamate transmission are quite different [for review, 20].

Similar to acute cocaine [101,159,165], an acute injection of methamphetamine elevates *Homer1a* mRNA expression in brain [158], which would be predicted to contribute to the acute psychomotor-activating effects of this drug [165]. While the capacity of methamphetamine to elevate *Homer1a* mRNA levels persists with repeated drug treatment, it does not increase with the development of behavioral sensitization [158]. Thus, like cocaine [237], the effects of repeated methamphetamine administration upon *Homer1a* mRNA expression do not easily account for this form of behavioral plasticity. A recent examination for the effects of repeated low dose (10×1 mg/kg) methamphetamine administration upon NAC Homer protein expression failed to detect changes in Homer1a/b/c or Homer2a/b at 24 h withdrawal. However, in contrast to repeated cocaine [168,227,236], repeated methamphetamine induces a marked increase in the NAC protein expression of all of these isoforms at 3 weeks withdrawal from repeated methamphetamine treatment (Table 2) [285]. These latter findings are more akin to those observed in mice treated repeatedly with alcohol [39,254,255], raising the possibility that the methamphetamine-induced reduction in glutamate receptor expression/function or other enduring deficits in corticoaccumbens glutamate transmission [e.g., 271,277–281] may elicit a compensatory rise in Homer expression. Deletion of either the *Homer1* or *Homer2* genes increases sensitivity to the psychomotor-activating effects methamphetamine [171], in a manner akin to that for cocaine [34,172]. While a cocaine-induced reduction in NAC CC-Homer expression is necessary to develop cocaine-induced behavioral and neurochemical sensitization [35], the functional consequences of the methamphetamine-induced increase in NAC Homer expression for methamphetamine-induced neuroplasticity remain elusive. However, as the data to date indicate that drug-induced changes in NAC Homer protein expression actively regulate the rewarding/reinforcing and/or psychomotor effects of cocaine and alcohol [34,35,39,172], methamphetamine-induced changes in NAC Homer protein expression may be involved in the enduring changes in behavioral sensitivity produced by this potent, psychomotor stimulant drug.

9. Stressor-induced regulation of Homers: implications for addiction vulnerability and relapse

Stress is highly implicated in the etiology of addiction and stressors are considered major precipitating factors in relapse to drug-seeking and -taking [cf., 151,152,221,286–294]. Like repeated drug administration (see above), repeated exposure to stressors induces morphological abnormalities within glutamatergic pyramidal neurons within the cortex of laboratory animals [e.g., 183,220,295–297]. Both psychological and physiological stressors can elevate corticoaccumbens glutamate levels [298–300] and repeated maternal stress elicits "cocaine-like" alterations in basal and cocaine-stimulated glutamate release within the NAC of adult offspring in conjunction with a "pre-sensitized" cocaine behavioral phenotype [294]. Evidence that stressors can affect the expression of Homers in brain was first described in the seminal report by Kato et al. [149], in which a modest rise in *Homer1a* mRNA expression was detected within hippocampal homgenates at 3 h following the systemic administration of the pharmacological stressors pentylenetetrazole and cycloheximide. Similarly, exposure to a mild stressor such as placement into a novel environment also augments *Homer1a* mRNA within hippocampus, as well as within parietal cortex

[301]. Intriguingly, Igaz et al. [302] reported no change in Homer1a protein expression within the hippocampus at 3 h following delivery of a mild footshock in a one-trial aversive learning paradigm; however, Homer1a protein expression was found to be elevated in animals sacrificed 24 h following shock delivery. This footshock-induced change in the pattern of Homer1a expression is very atypical for an IEG and is distinct from that produced by other forms of synaptic activity [101,149,301], raising the possibility that IEG Homers may regulate both the consolidation and recall of memories concerning stressful or aversive events [302].

In support of an enduring regulation of both IEG and CC-Homer expression by stressors, Homer1a, Homer1b/c and Homer2a/b protein levels were increased within the PFC, hippocampus and amygdala, while Homer1a levels were reduced in the striatum, of weanling offspring of rat dams subjected to repeated restraint stress during the last 7 days of gestation [156]. As these changes in Homer protein expression were observed at 3 weeks following the last maternal restraint stress, these data provide evidence that repeated prenatal stress can elicit persistent changes not only in CC-, but also, IEG-Homer expression, which are likely to impact synaptic development, morphology and plasticity. It remains to be determined whether or not the prenatal stress-induced alterations in IEG and CC-Homer expression persist into adulthood. However, prenatally stressed animals exhibit profound cognitive, social and sensorimotor deficits [303,304] and increased sensitivity to the psychomotor-activating, motivational and glutamate-sensitizing effects of stimulant drugs as adults [293,294,305]. Interestingly, the behavioral and glutamate phenotype induced by prenatal stress bears striking resemblance to that produced by *Homer1* deletion [34,171,172,306]. Thus, stressor-induced imbalances in IEG- and CC-Homer expression within corticolimbic structures may alter the development trajectory of cortico-limbic circuits, thereby increasing the propensity to develop addiction-related behaviors in later life [156,219].

10. Homers, addiction and schizophrenia co-morbidity

Patients with schizophrenia show alarmingly high rates of substance use disorders (20–65%) [307–312], as well as a considerably greater risk of developing a drug addiction disorder than individuals in the general population [313]. As reviewed in detail elsewhere [314], dually diagnosed schizophrenia patients typically present with more severe symptoms [307,308,315–318], exhibit increased suicidal ideation [319,320], require more frequent hospitalizations [309,321], and experience more frequent relapses than patients without co-occurring substance abuse [322–324]. While analyses for polymorphisms in the *Homer* genes have not yet been assessed in a co-morbid population, single nucleotide polymorphisms in *Homer1* have been associated with cocaine addiction [240], as well as in schizophrenia (IVS4 + 18A > G in intron 4) [325]. In addition to exhibiting increased sensitivity to the rewarding and psychomotor-activating effects of psychomotor stimulants, *Homer1* KO mice exhibit a host of other behavioral abnormalities, including deficits in working memory, pre-pulse inhibition of acoustic startle, instrumental learning and habituation to a mild stressor, as well as increases in emotional reactivity to mild stressors and behavioral despair [34,171,172,306]. Moreover, *Homer1* KO mice exhibit increased behavioral sensitivity to NMDA receptor antagonists [34,38,171] and both the deficit in pre-pulse inhibition and the increased sensitivity to phencyclidine can be reversed by pretreatment with either typical or atypical antipsychotic drugs [171; Richardson and Szumlinski, in preparation]. Coupled with their abnormal PFC glutamate phenotype (see above), the behavioral phenotype of *Homer1* KO mice is consistent with an animal model of schizophrenia [171,172]. It is highly unlikely that a single high penetrant mutation in *Homer1* accounts for cocaine addiction, schizophrenia or their high rate of co-morbidity; however, it is tempting to speculate that particular combinations of polymorphisms within *Homer1* or perhaps other *Homer* genes may contribute to, or increase the probability of, patients with schizophrenia developing a co-morbid substance abuse disorder.

11. Conclusions

The Homer family of postsynaptic proteins is critical for regulating the architecture of glutamatergic synapses within the brain and for maintaining normal glutamate tone within the corticoaccumbens pathway. Both pharmacological and non-pharmacological factors affecting addiction regulate IEG and constitutively expressed members of the Homer family of postsynaptic proteins within this pathway, as well as within other limbic structures implicated in the neurobiology of addiction. Behavioral and neural genetic studies provide preclinical evidence to support an important and active role for Homers in regulating drug-induced neuroplasticity, as well as cognitive and emotional processes associated with an addicted state. A significant association of single nucleotide polymorphisms within *Homer1* with cocaine addiction provides clinical support for *Homer* genes in addiction vulnerability and the continued application of mutational analysis techniques to examine for patterns of polymorphisms within the *Homer* gene family in addicted persons will provide opportunities to bridge preclinical and clinical knowledge regarding a role for these proteins in regulating addiction vulnerability and, perhaps also its treatment.

Acknowledgements

This work is supported, in part, by NIAAA grants AA-015351, AA-0135017 (INIA West) and AA-016650 (INIA West), the National Alliance for Research on Schizophrenia and Affective Disorders (NARSAD) and the University of California at Santa Barbara Academic Senate.

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