

Journal Club

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Addicted to Homer?

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Review of Szumlinski et al. (<http://www.jneurosci.org/cgi/content/full/25/30/7054>)

Drugs of abuse produce immediate reward effects as well as addiction. A major recent hypothesis is that addiction is a pathological learning process, involving synaptic plasticity in brain circuits that mediate the rewarding and behavioral effects of drugs (Kelley, 2004). Most drugs of abuse promote an increase in dopamine release at nerve terminals in the nucleus accumbens (NAcc), a key structure of the mesocorticolimbic dopamine reward pathway. Until recently, most attention was focused on dopaminergic transmission in the NAcc as a mechanism of addiction, but increasing evidence also implicates modulation of glutamatergic neurotransmission in the NAcc. Thus, proteins in the postsynaptic density (PSD) of glutamatergic synapses have emerged as candidate molecular mediators of the acute and chronic effects of drugs of abuse.

The Homer family of proteins is PSD scaffolding molecules associated with group 1 metabotropic glutamate receptors (mGluRs), NMDA receptors, and Ca^{2+} channels and therefore is critical for glutamatergic transmission (Fig. 1) (Ehrensgruber et al., 2004). Homer proteins are encoded by three genes (*Homer1–Homer3*). Several studies have linked Homer proteins to acute and chronic effects of cocaine. For example, during

withdrawal after repeated cocaine administration, there is a reduction in Homer1b/c expression in the rat NAcc (Swanson et al., 2001), and *Homer2* (H2)-deficient mice have a behavioral and neurochemical phenotype remarkably similar to that of cocaine withdrawal (Szumlinski et al., 2004). But do Homer proteins also drive addiction to other drugs? In the brain, ethanol acts on many cellular targets and has effects on almost every neurotransmitter system. One of the best characterized actions of ethanol is modulation of glutamatergic transmission. Ethanol exposure and withdrawal leads to an increase in extracellular levels of glutamate in the NAcc and modulates glutamate receptor function, including NMDA receptors. This link between glutamate and ethanol addiction led Szumlinski et al. (2005), in their recent *Journal of Neuroscience* paper (<http://www.jneurosci.org/cgi/content/full/25/30/7054>), to evaluate the role of Homer2 proteins in ethanol-induced behavior and neurochemical events induced by ethanol in the mouse NAcc.

To assess ethanol preference intake and the reinforcing properties of ethanol, the authors conducted an ethanol versus water preference test and an ethanol place-conditioning test in H2-deficient mice [H2 knock-out (KO)] and in wild-type (WT) mice. WT and H2KO mice displayed a preference for ethanol over water at 6% ethanol but not at 3% or 12% [Szumlinski et al. (2005), their Fig. 1A,B (<http://www.jneurosci.org/cgi/content/full/25/30/7054/FIG1>)]. Interestingly, at 12% EtOH, H2KO mice showed a stron-

ger preference for water than the WT mice. Moreover, WT mice exhibited a dose-dependent increase in place preference for the compartment where they received ethanol, whereas H2KO mice presented a place aversion [Szumlinski et al. (2005), their Fig. 1C]. Thus H2KO mice showed a reduced reward response to high ethanol concentrations. This effect is not a response to a general impairment of reward process, because H2KO mice were indistinguishable from WT mice for saccharine preference and food-induced place conditioning. Notably, reward to cocaine is enhanced in H2KO mice, not blunted (Szumlinski et al., 2004). Another way to evaluate ethanol sensitivity is to look at the effects of repeated ethanol injection on spontaneous locomotion. WT mice displayed locomotor depression after acute ethanol injection and displayed a behavioral adaptation (a decrease in this depression) after repeated ethanol injections [Szumlinski et al. (2005), their Fig. 2B (<http://www.jneurosci.org/cgi/content/full/25/30/7054/FIG2>)]. H2KO mice presented no such adaptation. Moreover, H2KO mice presented no differences in metabolism or pharmacokinetic tolerance to ethanol compared with WT mice [Szumlinski et al. (2005), their Fig. 2B]. These experiments demonstrated that Homer2 is necessary for ethanol-induced behavior. But is Homer2 also implicated in the neurochemical events involved in ethanol addiction?

Acute and chronic injections of ethanol increase extracellular levels of dopamine and glutamate in the mouse NAcc. Using *in vivo* microdialysis experiments,

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Szumliński et al. (2005) evaluated the extracellular levels of dopamine and glutamate in the NAcc of H2KO and WT mice. Before ethanol injections, the extracellular level of dopamine was the same in WT and H2KO mice, but the level of glutamate in H2KO mice was 50% of that seen in WT mice [Szumliński et al. (2005), their Table 1 (<http://www.jneurosci.org/cgi/content/full/25/30/7054/TBL1>) and Fig. 3 (<http://www.jneurosci.org/cgi/content/full/25/30/7054/FIG3>)]. After repeated injections, the extracellular levels of dopamine and glutamate were increased in WT mice but not in the H2KO mice. Thus, Homer2 expression is required for the characterized ethanol neurochemical adaptations in the NAcc. Ethanol is also known to inhibit NMDA receptor functions, and human genetic studies link ethanol addiction vulnerability to an alteration in NMDA receptor sensitivity. Thus the authors assessed the sensitivity of the H2KO mice to NMDA receptor blockade. They microinjected 3-(2-carboxypiperazin-4-yl) propyl-1-phosphonic acid (CPP), a competitive NMDA receptor antagonist, into the NAcc and found that CPP induced a larger increase in locomotor activity in H2KO mice than in WT mice [Szumliński et al. (2005), their Fig. 4A (<http://www.jneurosci.org/cgi/content/full/25/30/7054/FIG4>)]. This effect was correlated with modifications in the level of NMDA receptors, because H2KO mice displayed a decrease in the NAcc membrane level expression of NR2A [Szumliński et al. (2005), their Fig. 4B]. Finally, to confirm that the phenotype observed in H2KO mice was directly linked to the defect in Homer2 expression and not to an adaptation of brain circuitry, the authors performed the same behavioral tests and neurochemical measurements in H2KO mice 3 weeks after infusing an adeno-associated virus encoding for Homer2b (AAV-H2) in the NAcc. The AAV-H2 infusion rescued the differences in EtOH-induced behavior and neurochemical adaptations between WT and H2KO

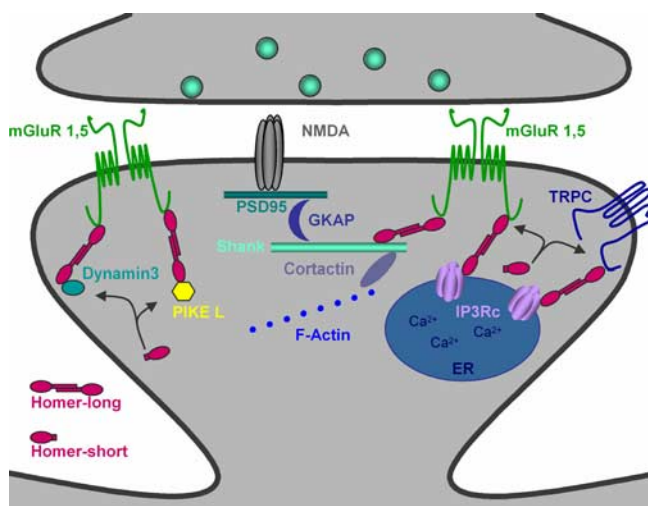


Figure 1. Schematic representation of Homer and its major binding partners at the glutamatergic PSD. Homer proteins can interact with a poly-proline consensus binding motif present on the C terminus of group 1 metabotropic glutamate receptors (mGluR1 and mGluR5), the shank family of proteins, the inositol-1,4,5-triphosphate receptors (IP3Rc), a phosphoinositide 3-kinase enhancer (PIKE L), the C-type transient receptor potential (TRPC) channels, and dynamin 3. NMDA receptors are in turn linked to the shank family of proteins via PSD-95 and the guanylate-kinase associated proteins (GKAP). The shank family of proteins is also linked to the actin cytoskeleton by the cortactin. The long Homer isoforms contain a coiled-coil (CC) domain followed by leucine zipper motifs at their C terminus. This allows the formation of homo- and hetero-oligomeric complexes and a cross-linking between the different Homer binding partners. In contrast, the short Homer isoforms lack the CC domain and are unable to multimerize, thereby acting as a natural dominant negative.

mice [Szumliński et al. (2005), their Figs. 5 (<http://www.jneurosci.org/cgi/content/full/25/30/7054/FIG5>) and 7 (<http://www.jneurosci.org/cgi/content/full/25/30/7054/FIG7>)]. Thus Homer2b loss is the specific source of the defects observed in H2KO mice related to ethanol addiction.

In conclusion, the results presented by Szumliński et al. (2005) demonstrate, *in vivo*, a new role for the Homer family of proteins in drug addiction. Homer2 appears to be a key player in both cocaine- and ethanol-induced addiction. However, the molecular and cellular mechanisms linking Homer2 to the acute and chronic effects of these different drugs are still obscure. Dissecting further the specific cellular adaptations induced by each of these drugs is of great importance to identify precise therapeutic targets for effective prevention and treatment of addiction.

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