GPCR Interacting Proteins (GIPs) in the Nervous System: Roles in Physiology and Pathologies

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Annu. Rev. Pharmacol. Toxicol. 2010. 50:89–109

First published online as a Review in Advance on September 30, 2009

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

This article's doi: 10.1146/annurev.pharmtox.010909.105705

0362-1642/10/0210-0089$20.00

Annu. Rev. Pharmacol. Toxicol. 2010.50:89-109.

Key Words

signal transduction, mutiprotein complex, neurological disorder, psychiatric disorder

Abstract

G protein-coupled receptors (GPCRs) are key transmembrane recognition molecules for regulatory signals such as light, odors, taste hormones, and neurotransmitters. In addition to activating guanine nucleotide binding proteins (G proteins), GPCRs associate with a variety of GPCR-interacting proteins (GIPs). GIPs contain structural interacting domains that allow the formation of large functional complexes involved in G protein-dependent and -independent signaling. At the cellular level, other functions of GIPs include targeting of GPCRs to subcellular compartments and their trafficking to and from the plasma membrane. Recently, roles of GPCR-GIP interactions in central nervous system physiology and pathologies have been revealed. Here, we highlight the role of GIPs in some important neurological and psychiatric disorders, as well as their potential for the future development of therapeutic drugs.

INTRODUCTION

G protein-coupled receptors (GPCR): seven transmembrane proteins activated by numerous extracellular signals, which catalyze the GDP/GTP exchange on heterotrimeric guanine nucleotide binding proteins

GPCR-interacting proteins (GIPs): proteins that bind directly to GPCRs and modulate their trafficking, membrane targeting, and signaling pathways

β-arrestins: GIPs that bind to activated/phosphorylated GPCRs and block G protein activation, trigger GPCR endocytosis, and scaffold signaling molecules, leading to induction of intracellular signaling

Homer proteins: GIP family that binds to many signaling molecules (including mGluRs). Only the long forms can self-aggregate via their coiled-coil domain

Unicellular or higher-order organisms discriminate and sense environmental stimuli to generate appropriate physiological responses. Extracellular signals such as light, odors and taste, or intercellular signals such as hormones and neurotransmitters are mainly, although not exclusively, detected by seven transmembrane cell surface G protein-coupled receptors (GPCRs). During evolution, molecular tinkering of one or few ancestral genes has been necessary to facilitate the recognition of a large number of different chemical signals. The success of this evolutionary tinkering was splendid, because approximately 1000–1500 genes that encode GPCRs are found in many genomes including *Caenorhabditis elegans*, rodents, and humans (1, 2). Researchers thought that GPCRs were part of a "two-dimensional" signaling pathway (3). In this formulation, ligand-activated GPCRs mobilize a limited number of G proteins composed of Gα and Gβγ subunits, and GPCR-catalyzed guanosine diphosphate (GDP)-guanosine triphosphate (GTP) exchange on Gα induces dissociation of the G protein into two entities: Gα-GTP and Gβγ. One or both of these entities then stimulate or inhibit second messenger production and/or ionic channel activities.

According to Paul Valéry, "What is simple is certainly wrong." Indeed, the control of cell physiology by GPCRs is far more complex. First, the dissociation of Gα-GTP from Gβγ subunits does not always occur and may not be complete (4). Second, in addition to G proteins, the environment of GPCRs includes a large number of GPCR-interacting proteins (GIPs) assembled into functional complexes (5–8). GIPs control GPCR subcellular localization, as well as the nature, kinetics, strength, and fine-tuning of GPCR signaling. Thus, in neurons, GIPs not only regulate GPCR targeting to subcellular compartments, but also their trafficking in and out of the plasma membrane, within the endoplasmic reticulum, Golgi apparatus, endosomal, and lysosomal compartments during synthesis, endocytosis, recycling, and degradation. In addition to GPCRs, GIPs can cluster various proteins; thus coordinating positive and negative feedback signals, creating molecular threshold, graded, or digital signals, as well as transient, sustained, or oscillatory signaling (9, 10). Some GIPs trigger events that are independent of G protein activation, as has been well demonstrated for β-arrestin (β-Arr) signaling (11–13). Recent reviews have provided an inventory of GIPs and their various functions in cellular physiology (5, 6). Here, we highlight the implication of GIPs in higher CNS functions, neurological disorders, and psychiatric disorders, as well as their potential for future development of therapeutic drugs.

MGLUR1,5-HOMER INTERACTIONS: A CRUCIAL LINK FOR GROUP I MGLUR-INDUCED SYNAPTIC PLASTICITY AND FRAGILE X MENTAL RETARDATION SYNDROME

Homer proteins are the products of three genes in mammals, one gene in *Xenopus*, and one gene in *Drosophila* (14, 15). Each *Homer* gene is alternatively spliced. A common characteristic of all generated Homer proteins is the presence of an EVH1 (Ena/Vasp homology) N-terminal domain that binds to a proline-rich sequence (PPSPF) found in signaling molecules of neurons, skeletal myocytes, and T-cells (16, 17). Homer-associated proteins include Group I metabotropic glutamate receptors type 1 and type 5 (mGuR1,5), inositol-1,4,5-triphosphate (IP3) receptors, ryanodine receptors, transient receptor channel-1 and 4 (TRPC1, TRPC4), $Ca_v2.1$ subunit of P/Q-type Ca^{2+} channels, the major postsynaptic scaffolding protein Shank, the phosphoinositide 3-kinase (PI3K) enhancer-long (PIKE-L) (18), Dynamin III, and the nuclear factor of activated T cells (NFAT) (5, 8, 16). The long forms of Homer proteins are also characterized by the presence of a central hinge region followed by a C-terminal coiled-coil domain that is probably organized in two separate regions: CC1 and CC2 (19). These proteins are constitutively expressed and act as scaffolds to crosslink and regulate the functions of their partners. They form a tetrameric Hub structure

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composed of two antiparallel dimers at the glutamatergic postsynaptic density (19). This structure confers slow turn-over rates and great efficiency in coordinating spine functions to Homer proteins. Shank proteins (Shank1) are also assembled in high-order complexes through self-association of their C-terminal SAM domain. Together with Homer multimers, they form a platform in spines (20) (**Figure 1**) that integrates the GKAP-PSD-95-NMDA ionotropic glutamate receptor assembly, the CaV1.3 subunit of L-type Ca^{2+} channels, the β-PIX-GIT1-PAK trimeric complex (which controls spine formation via activation of Rac,Cdc42, and/or RnD1), the cytoskeletal proteins cortactin, sharpin, fodrin, Abl-1, dynamin-2, and other GPCRs, such as somatostatin receptors (SSTR2) and the calcium-independent receptor for alpha-latrotoxin (CIRL1–2).

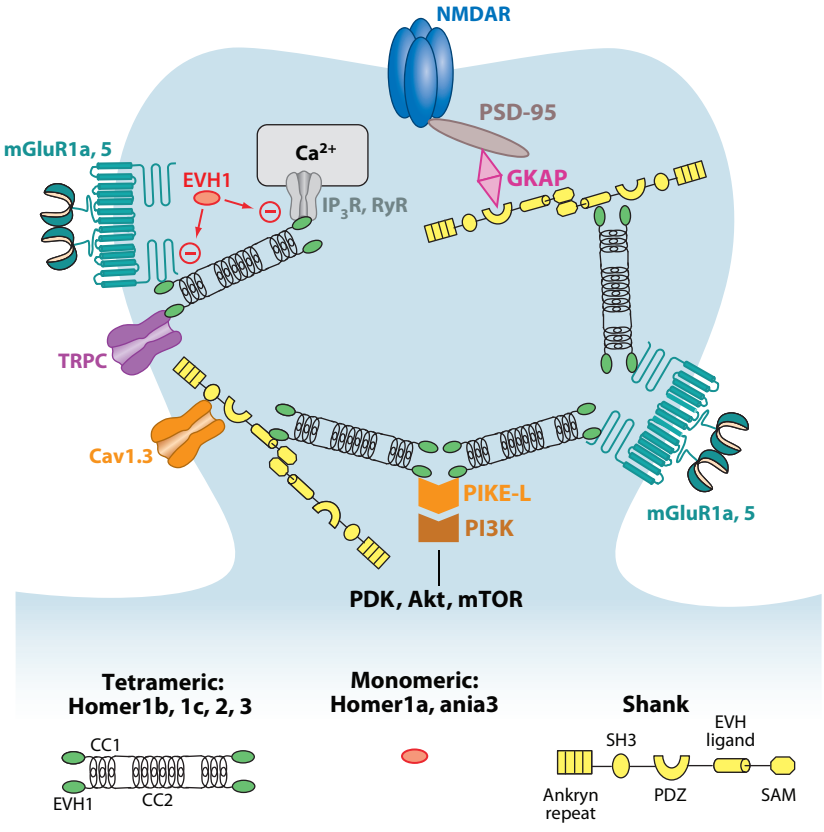

Figure 1

Two Homer proteins interact with each other to form a dimer, and two antiparallel dimers form a tetrameric unit. Coiled-coil domains (CC1 and CC2) support this tetrameric organization of Homer1b, 1c, 2, 3 (*bottom left*). Shank proteins (*bottom right*) interact with each other through their SAM (sterile alpha motif) domain and form a postsynaptic multimeric platform. By interacting with each other, the Shank and Homer complexes form a network of higher order complexity. This network assembles ionotropic (NMDA) and G protein-coupled (mGluR1a, 5) glutamate receptors, as well as membrane (TRPC and Cav1.3) and intracellular (IP3 and ryanodine receptors, IP3R/RyR) Ca^{2+} channels (*left*). The IP3R/RyR are part of the intracellular signaling of mGluR1a, 5 (*top left*). The Homer-Shank platform integrates these receptors and channels with other intracellular signaling pathways, such as the PIKE-L/PI3K pathway (*bottom*) that mobilizes a PDK-Akt-mTOR signaling that is responsible for mRNA translation in LTD. The Homer1a/ania-3 protein is composed of only the EVH1 domain of Homer proteins (*bottom*) and therefore is found solely as a monomer. It competes with coiled-coil Homer-mediated interactions (*top left*).

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The short forms of Homer proteins, Homer1a and ania-3 (a *Homer3* splice variant) (**Figure 1**), are characterized by the absence of the coiled-coil domain, a rapid synthesis similar to that observed for other immediate early genes (IEG) following elevated synaptic activity, as well as in response to acute or chronic use of drugs of abuse such as cocaine, amphetamine, LSD, phencyclidine (PCP), and nicotine (14, 15, 21, 22). The short forms of Homer act as endogenous dominant-negative disrupting protein complexes that are linked by the long forms of Homer. This inhibitory action has many cellular physiological consequences. First, it induces an agonist-independent/constitutive activation of mGluR1 (23) and TRPC1 channels (24). Second, it inhibits a form of synaptic plasticity called long-term depression (LTD) that is essential for learning and memory (25), drug-induced neuroplasticity, epilepsy, and chronic pain (21, 26).

Long-term potentation (LTP) and long-term depression (LTD): synaptic plasticity events that increase (LTP) or decrease (LTD) the strength of synaptic transmission for long periods and believed to support the molecular basis of learning and memory

Fragile X mental retardation protein (FMRP): Protein encoded by a gene silenced by hypermethylation in the Fragile X syndrome, which locally regulates protein synthesis at synapses

Long-lasting changes in synaptic strength have strong implications in neurological diseases. Among these diseases, Fragile X mental retardation (FMR) is the most common inherited disease that causes mental retardation (27). This disorder is caused by the expansion of the trinucleotide sequence CGG in the 5′ UTR of the FMR1 gene on the X chromosome, which leads to hypermethylation and silencing of the FMR1 gene. The Fragile X mental retardation protein (FMRP) is found in dendrites, where it binds to a subset of mRNA-encoding proteins involved in synaptic plasticity and development, and inhibits their translation (28, 29).

Activation of group I mGluRs was reported to rapidly stimulate the synthesis of FMRP in synaptoneurosomes (30). In the absence of FMRP, exaggerated mGluR signaling could be responsible for diverse psychiatric and neurological symptoms of the Fragile X syndrome, including delayed cognitive development, seizures, anxiety, movement disorders, and obesity (31). Excessive sensitivity to environmental change, synaptic connectivity, protein synthesis, memory extinction, body growth, and excitability of the Fragile X syndrome can all be corrected by reducing mGluR5 activity (32) or synthesis (33), thus supporting the theory that the Fragile X syndrome results from unbalanced activation of Group I mGluRs and impaired synaptic maturation (34).

Impairment of long-lasting synaptic plasticity is the cellular basis underlying FMR. MGluR-induced LTD is protein synthesis-dependent (35) and involves, in part, the internalization of AMPA glutamate receptors (36). MGluR-dependent LTD induces an irreversible loss of ionotropic (AMPA) glutamate receptors that could be a prelude to synapse elimination (36, 37). In *Fmr1* KO mice, mGluR-induced LTD is enhanced, which might lead to a loss of synaptic contacts and to cognitive disorders (38–41). Paradoxically, in these mice models, mGluR-induced LTD is independent of protein synthesis (30, 38, 42, 43), possibly due to a weaker association of the receptor with Homer proteins (44). In the absence of regulation of mRNA translation by FMRP, alternative mGluR-induced LTD mechanisms, in particular ones that do not require de novo protein synthesis and use proteins accumulated in dendrites, contribute to AMPA receptor endocytosis (41). Interaction of mGluR5 with Homer is required for induction of the translational machinery responsible for the mGluR-dependent LTD (25). Another consequence of the weaker association of Homer with mGluR5 in *Fmr1* KO mice is a reduced negative regulation of this association by Homer1a. Because Homer1a induction might function to oppose epilepsy and anxiety, its reduced negative regulation might contribute to the epilepsy and anxiety symptoms observed in patients with Fragile X mutations.

IMPLICATION OF THE MGLUR1-HOMER INTERACTIONS IN SCHIZOPHRENIA, ANXIETY, AND ATTENTION DEFICITS

Homer1, but not *Homer2*, KO mice exhibit a phenotype that is consistent with an animal model of schizophrenia (22, 45). The animals display a deficit in prepulse inhibition of acoustic startle and increased sensitivity to phencyclidine, an NMDA receptor antagonist that induces psychomimetic

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behavior. Both effects are reversed by pretreatment with typical and atypical antipsychotics. Surprisingly, both psychomimetic and antipsychotic drugs stimulate IEG Homer1 isoforms. Moreover, a single nucleotide (22) polymorphism (SNP) in the intronic sequence of Homer1 (IVS4 +18 A >G in intron 4) is associated with cocaine addiction and schizophrenia (46). The high rate of comorbidity between schizophrenia and substance use disorders (20–65%) may be based on this polymorphism to some extent (21). Shank3 binds indirectly to group I mGluRs (**Figure 1**), but also directly to the somatostatin SSTR2 receptor and other adaptor and signaling proteins of the spine that have been found to be mutated in patients suffering from a familial form of autism (47). Similar to schizophrenia, autism is now thought to result from abnormal brain development (47a, 47b). These neuropsychiatric disorders are often associated with an increase in stress and anxiety. *Homer1*, but not *Homer2*, deletion is associated with anxiety and behavioral responses to stressors in mice (21). This is not due to the absence of *Homer1*, but rather to the inability of *Homer1* KO mice to induce Homer1a protein expression that normally occurs under these conditions. Restoration of Homer1a and Homer1c expression, using targeted gene transfer in the prefrontal cortex (PFC), reduces anxiety and reinforces stress, respectively (21, 22). In contrast, the cognitive and attention deficits observed in *Homer1* (but not *Homer2*) KO mice, are restored by expression of Homer1c (but not Homer1a) in the PFC (22).

HOMERS, NEUROPLASTICITY, AND ADDICTION

In addition to their scaffolding of ionotropic and metabotropic receptors, Homer proteins are essential for physiological homeostasis of glutamatergic synapses (8, 14). This role may be essential during acute and chronic action of drugs of abuse such as cocaine and alcohol, particularly in the PFC-nucleus accumbens (NAc) glutamatergic pathway. Expression of Homer proteins is dynamically regulated in these structures. Three weeks after withdrawal from repeated cocaine administration, Homer1b/c and Homer2a/b content drastically decreases (−50%) in the NAc, whereas Homer2a/b content but not that of Homer1b/c increases in the PFC (21). *Homer1* and *Homer 2* KO mice display increased locomotion sensitization to cocaine, conditioned reward, and extracellular glutamate in NAc following withdrawal from repeated cocaine administration. On the other hand, *Homer1* (but not *Homer2*) deletion increases PFC glutamate content. How these proteins induce such pronounced changes in glutamate content is not clear but a role of the cystine-glutamate antiporter has been proposed (48). Restoration of the content of long forms of Homer proteins in the NAc of Homer KO mice prevents locomotor sensitization that follows repeated cocaine administration (48). Homer2 is an important facilitator of alcohol-induced behavioral changes, including alcohol drinking. Thus, Homer2 KO mice exhibit an alcohol-avoiding and alcohol-intolerant phenotype (21).

IMPLICATION OF HOMER1a IN EPILEPSY

In the rat kindling model of temporal lobe epilepsy, repeated electrical stimulation of the amygdala resulted in the differential expression of 264 genes in the hippocampus, as compared to sham controls. Among these genes, *Homer1a* was the most strongly induced one (49, 50). These observations raise the issue of a potential role of this protein in epilepsy. Transgenic mice that overexpress a constitutive mosaic Homer1a within the hippocampus exhibit lowered seizure susceptibility and retarded kindling (50). Consistent with this result, viral infection with Homer1a, but not Homer1c, suppresses status epilepticus induced by continuous focal electrical stimulation within the hippocampus (51). These data suggest an inhibitory role for Homer1a in the generation and propagation of seizures. A mechanism has been proposed for this effect. Injection of Homer1a

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protein in neocortex pyramidal cells reduces membrane excitability, an effect abolished by the mGluR5 antagonist MPEP involving intracellular IP3-mediated signaling and Ca^{2+}-activated membrane K^+ channels (52). Homer1a is also induced by electroconvulsive stimulation in the rat (53, 54). Interestingly, reduction of excitability was also observed following electroconvulsive shocks and this effect was antagonized by anti-Homer1a, but not anti-Homer1b/c antibodies, thus implicating the immediate early gene Homer1a but not the constitutively expressed Homer1b/c homolog. Upon electrically induced seizures, an increase in Homer1a expression would directly activate mGluR1a/5 independent of glutamate binding to the receptor, thereby resulting in IP3-dependent intracellular Ca^{2+} release, opening of Ca^{2+}-dependent K^+ channels, and membrane hyperpolarization. Indeed, decoupling mGluR1a/5 from long forms of Homer with Homer1a results in their constitutive activation, an effect independent of stimulation with glutamate (23). Homer1a might therefore act as an intrinsic antiepileptogenic and anticonvulsive agent that would counteract progression of the seizures (52). Electroconvulsive shock has been an established but poorly understood therapy for psychiatric disorders. An unanswered question is the extent to which an increase in Homer1a expression induced by the electrical stimulations might account for the clinical efficacy of this treatment.

Protein interacting with C Kinase 1 (PICK1): atypical PDZ domain-containing protein that interacts with the C-terminus of glutamate receptors (mGluR7 and GluR2), ionic channels, transporters, and PKC

PDZ (PSD-95-disc large-zonula occludens) domain: protein-protein interaction domain that binds to short peptide motifs (PDZ ligands) localized at the extreme carboxy-terminus of their target proteins

IMPLICATION OF HOMER IN INFLAMMATORY PAIN

Homer1a is rapidly induced in spinal cord neurons, but not in the corresponding presynaptic nociceptive dorsal root ganglia (DRG) neurons, during inflammatory pain (26). Homer1a synthesis is triggered by the ERK/Src kinases signaling pathway following NMDA receptor activation. Consecutive Homer1a-induced disruption of constitutive long form Homer-based complexes induces a strong reduction in the density of dendritic spines and an attenuation of glutamate-induced Ca^{2+} mobilization in spinal neurons, which are known to process pain inputs. Inhibition of Homer1a synthesis by shRNA exacerbates inflammatory pain. Targeted gene transfer of Homer1a in spinal neurons reduces inflammatory pain without significantly affecting physiological pain, locomotion or motor coordination. These observations strongly implicate Homer1a as a therapeutic target for inflammatory pain (26).

IMPLICATION OF MGLUR7-PICK1 INTERACTION IN SYNAPTIC TRANSMISSION, SYNAPTIC PLASTICITY, AND NEUROLOGICAL DISORDERS

PICK1 (protein interacting with C kinase 1) has been cloned from a yeast two-hybrid screen as a peripheral membrane protein that interacts with protein kinase Cα (PKCα) (55). The mGluR4, mGluR7a/b and mGluR8b glutamate receptor subtypes are the only GPCRs among the 40 proteins that have been identified to interact with PICK1 (56). Interaction with these receptors occurs through their C-terminal PSD-95-disc large-zonula occludens (PDZ) domains (57).

PICK1 regulates the trafficking and synaptic aggregation of AMPA receptors (58–60) and mGluR7 through phosphorylation by PKCα (61–63). The mGluR7 is mainly localized at glutamatergic and GABAergic axon terminals. Because of its low affinity for glutamate, this receptor is thought to be activated only upon high frequency synaptic activity and elevated glutamate release (64). Once activated, mGluR7 inhibits presynaptic P/Q type voltage-sensitive Ca^{2+} channels via a G protein- and PKC-dependent pathway. This downregulates neurotransmitter release and synaptic activity. Importantly, this negative feedback requires interaction of mGluR7a with PICK1 (65).

An interesting issue has been to identify the functional role of PICK1 in integrated neuronal networks. In hippocampal slice preparations, mGluR7 activation, combined with high frequency

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stimulation of the hippocampal mossy fiber–stratum lucidum interneuron synapse, triggers a presynaptic LTD that results from persistent P/Q type Ca^{2+} channel inhibition. We speculate that this effect involves PICK1-dependent coupling of the receptor with PKC. Interestingly, following pharmacological internalization of mGluR7 (desensitization), high-frequency stimulation then produces presynaptic LTP. This form of metaplasticity is not a simple reversal of Ca^{2+} channel inhibition, but a cAMP-PKA- and RIM1α-dependent presynaptic mechanism instead (66).

Metaplasticity: refers to activity-dependent changes in neuronal functions that modulate subsequent synaptic plasticity such as LTP or LTD

The function of PICK1 in whole organisms is only partially understood. PICK1 KO mice display deficient AMPA receptor trafficking and synaptic plasticity (67, 68), but whether this is accompanied by a learning and memory deficit has not been studied. More information is provided by in vivo studies. Rats and mice injected with a cell permeable mimetic peptide that specifically disrupts the interaction between mGluR7a and PICK1 display a phenotype characteristic of a particular form of epilepsy: absence epilepsy (**Figure 2**). A similar phenotype is observed in PICK1 KO mice and in transgenic mice expressing mGluR7a with a mutation in the PDZ ligand for PICK1 (69). The epileptic phenotype is accompanied by high susceptibility to the convulsive drug pentylenetetrazole, and by working memory deficits (64, 70, 71).

Thus far, no alteration in the *PICK1* and/or *MGR7* (coding mGluR7) genes has been associated with epilepsy or any other neuropsychiatric disease in humans, except for schizophrenia. The human *PICK1* gene is located in the 22q13.1 chromosome, a region that has been associated with schizophrenia (72–75), and polymorphisms of this gene have been found in schizophrenic patients (76).

IMPLICATION OF β-ARRESTINS-AKT-GSK3 IN MONOAMINERGIC RECEPTOR-ACTING DRUGS

Most mammalian tissues, including brain, express β-Arr1 and β-Arr2, whereas visual cones and rods express arrestin homologs. Activated GPCRs recruit β-Arrs. β-Arrs function as a platform that assembles an endocytotic complex, which internalizes GPCRs mostly in clathrin-coated pits (12). β-Arrs have many other functions. It is now clear that apart from their action on G proteins, GPCRs can also elicit cellular responses mediated by the formation of signaling protein complexes scaffolded by β-Arrs (77). GSK3α and GSK3β are constitutively active kinases that are inhibited following their phosphorylation by different kinases, such as Akt, in response to hormones and growth factors including insulin. Stimulation of dopamine D_2 receptor, either directly with apomorphine (a nonselective dopaminergic agonist) or indirectly in dopamine transporter KO mice, results in the inhibition of Akt activity and concomitant activation of GSK3 in striatum (78, 79). The effects of D_2 receptors on Akt/GSK3 kinase activities do not seem to be mediated by second messengers, but rather by β-Arrs because they are absent in β-Arr2 KO mice (79). The mechanism of action of D_2 receptors involves the formation of a protein complex comprising Akt, β-Arr2, and the protein phosphatase PP2A that facilitates the dephosphorylation and thus the inactivation of Akt (78). In line with these observations, there is evidence for a crucial role of the β-Arr2/Akt/GSK3 signaling pathway in behavioral effects of indirect and direct activation of D_2 receptors. These include apomorphine-induced climbing and amphetamine-induced locomotor hyperactivity (79). Blockade of D_2 receptors with the antipsychotic haloperidol enhances Akt phosphorylation and decreases GSK3 activity (80). Acute or subchronic administration of atypical antipsychotics, such as clozapine and olanzapine, also inhibits GSK3 (81, 82). These drugs block D_2 receptors but also display high affinity for the 5-HT_{2A} receptor. Stimulation of 5-HT_{2A} receptors activates GSK3 via an unknown signaling pathway (81). Thus, it is possible that the therapeutic effect of typical and atypical antipsychotic drugs depends on GSK3 inhibition, but by different routes. The Wnt pathway is upstream of GSK3 and has also been implicated

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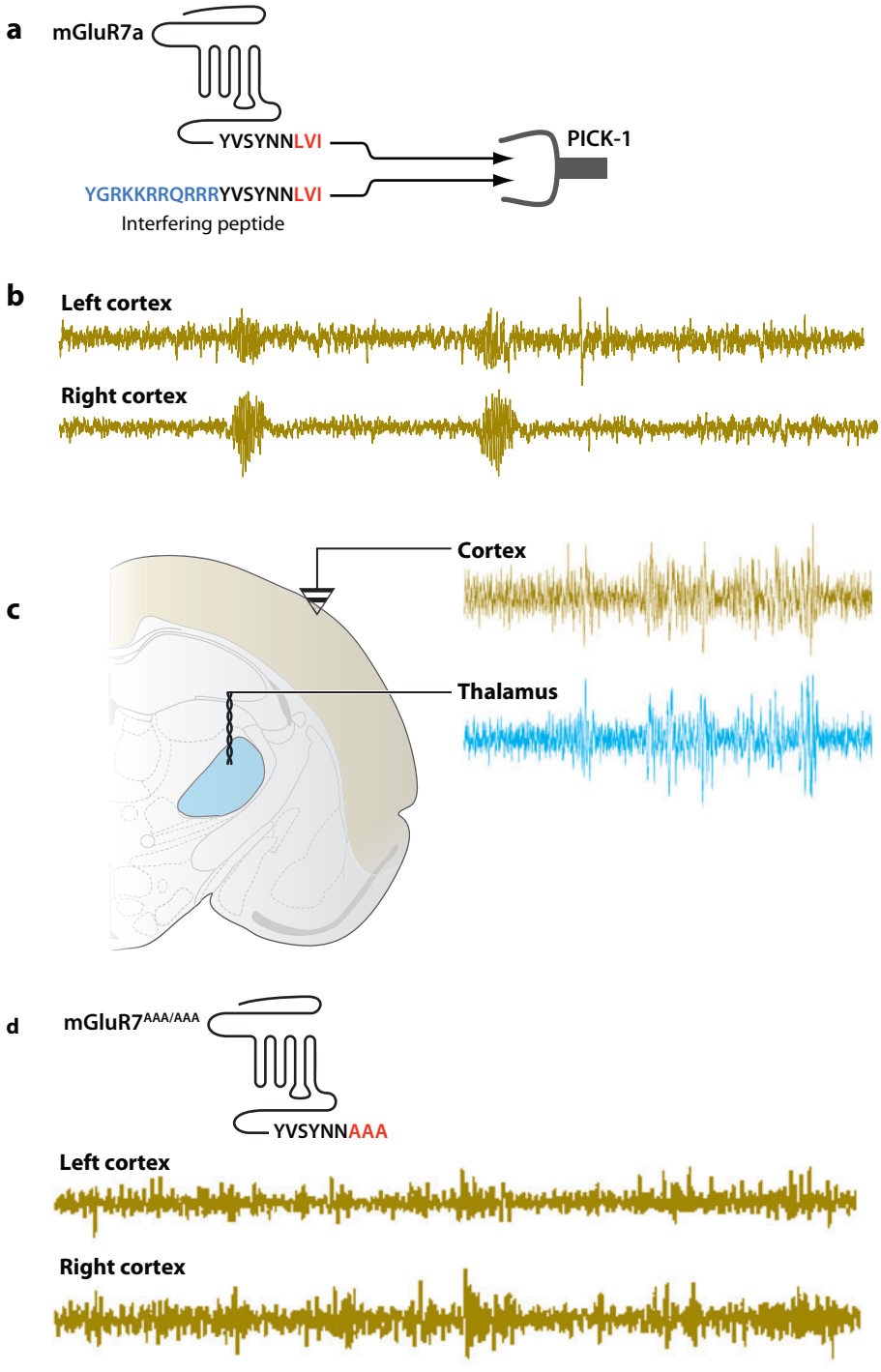

Figure 2

The mGluR7a receptor displays a C-terminal PDZ-binding motif (LVI, *in red*) that is recognized by PICK1. The interaction between the two proteins can be disrupted by a peptide mimicking the mGluR7 C-terminal sequence. This interfering peptide was fused to the transduction sequence of the HIV TAT protein (*blue*) (*a*) and applied systemically to mice and rats. This induced electroencephalographic paroxysmic cortical discharges that are typical of absence epilepsy. These discharges were synchronous between the left and right cortex (*b*) as well as between the cortex and thalamus (*c*). Similar epileptic activity can be recorded in a noninjected transgenic mice mutated on the PDZ-interaction motif of the mGluR7a receptor (*d*). (Modified from Bertaso et al. 2008). Abbreviations: Cx, cortex; Th, thalamus; Hi, hippocampus; Am, amygdala.

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in antipsychotic drug effects (83). Lithium is one of the most prescribed drugs for the treatment of bipolar disorders. Although lithium inhibits GSK3 directly, it also activates Akt and destabilizes the Akt/β-Arr2/PP2A complex, thereby inactivating GSK3 (79, 84). The effect of Akt/GSK3/β-Arr2 in signaling and behavioral response to dopamine/5-HT receptors, lithium, and antipsychotic drugs may indicate a role of these molecules in schizophrenia and cognition. A significant association of an Akt1 haplotype with schizophrenia has been found in several cohorts of schizophrenic patients from different origins (79).

Disrupted-in-schizophrenia (DISC1) and neuroregulin1 (NRG1) are two schizophrenia susceptibility gene-encoded proteins that affect Akt phosphorylation. Akt protein content is reduced in brains of schizophrenic patients (79). In addition, GSK3 has been implicated in synaptic plasticity and trafficking of NMDA receptors (79). It has been recently proposed that GPCRs can be stabilized in different active conformational states depending on the nature of the agonist, a phenomenon called "ligand-directed trafficking or signaling" (85). A particularly interesting example of agonist-directed signaling is the signaling induced by hallucinogens (such as LSD, DOI, (-)DOB) versus non-hallucinogen agonists (such as lisuride) upon activation of 5-HT_{2A} receptors. Both ligand categories stimulate the G_q/G_{11}/PLC pathway leading to *c-fos* induction (86, 87). In contrast, only hallucinogenic drugs activate the G_i/G_o/Src pathway and induce the *egr-2* gene (87). In addition, high concentrations of endogenous 5-HT (following 5-hydroxytryptophan treatment) induces a head twitch response in mice (taken as an index of hallucinogenic 5-HT drugs in humans), which is β-Arr2 dependent (88). On the other hand, DOI induces a similar behavior, but in a β-Arr2-independent manner (88). Concomitantly, ERK 1/2 activation by 5-HT largely requires β-Arr2, whereas ERK1/2 activation by DOI is independent of β-Arr2. This suggests that the 5-HT_{2A} receptor-β-Arr2 complex can mediate signaling events via different mechanisms, depending on whether the 5-HT_{2A} receptor is occupied by 5-HT or DOI. Of note, the 5-HT_{2A} receptor bound to 5-HT activates GSK3β, whereas no activation was observed when this receptor was occupied by DOI (81). Such differing effects of 5-HT receptor-active agents may have major implications in the development of drugs for the treatment of schizophrenia.

Glycogen synthase kinase (GSK) 3α and β: serine/threonine protein kinases; substrates of Akt

Akt: serine/threonine protein kinase activated downstream of phosphatidylinositol 3-kinase (PI3-K). PI3-K phosphorylates the inositol ring of phosphatidylinositol-4,5 P (PtdIns-4,5P) to generate PtdIns-3,4,5-P (PIP3)

Spinophilin: dendritic spine-enriched protein that interacts with several GPCRs including dopamine D2 receptors and μ-opioid receptors as well as other components of GPCR signaling cascades

IMPLICATION OF β-ARRESTINS AND SPINOPHILIN IN OPIATE SIGNALING, TOLERANCE, DEPENDENCE, AND ADDICTION

Opiates and particularly morphine are powerful pain relievers. However, repeated exposure to these drugs leads to tolerance that is characterized by reduced analgesic efficacy and often viewed as the gateway to the development of physical and psychological dependency. Physical dependency can be evaluated by withdrawal symptoms such as jumps, wet-dog shakes, diarrhea, and weight loss. Addiction is characterized by an exacerbated dependency and withdrawal, craving, and persistent sensitivity to relapse, even after the disappearance of withdrawal symptoms. In addition, some drug abusers are less sensitive to drug addiction than others. The molecular mechanisms of opiate tolerance and dependency have been intensely evaluated but remain largely obscure. The μ-opioid receptor (MOR) is the main participant in drug of abuse-induced pathologies, but several other associated players are important. These are adenylyl cyclases, G protein receptor kinases (GRKs), regulators of G protein signaling (RGS), and, central to this review, β-Arrs and spinophilin (78, 88–92). Spinophilin is a neuronal spine-enriched protein that interacts with protein phosphatase 1 (PP1), RGS proteins, and dopamine D_2 receptors (93). Spinophilin also modulates an α_2-adrenergic–Gβγ complex and antagonizes β-Arr2 function (94). In addition, under basal condition, spinophilin forms a complex with MOR, GRK2, Gβ5 (the Gβ in the striatum), and RGS9–2 proteins (95).

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A major question is why some MOR agonists such as morphine induce more tolerance and dependency than other agonists such as etorphine, fentanyl, or methadone. A key observation is that in heterologous cell lines, but also in vivo, morphine is quite poor at facilitating MOR endocytosis (91). In HEK-293 cells, there is an inverse correlation between the capacity of MOR agonists to induce endocytosis, and to promote desensitization and their ability to induce tolerance (90). Although endocytosis of MOR is higher in neurons than in HEK-293 cells (96), most likely because of higher content of GRKs, β-Arr, and spinophilin (95), morphine-activated MOR is more resistant to desensitization and endocytosis than enkephalin- or other opiate-activated MOR. Moreover, the endocytotic pathway is necessary for efficacious recovery of GPCR activity via recycling (91). Thus, morphine-activated MOR, possibly associated with β-Arrs, remains at the cell surface for a longer period of time. This may account for higher tolerance, because these receptors will not be resensitized. Indeed, β-Arr2 KO mice are resistant to MOR desensitization and do not develop antinociceptive tolerance in the hot plate test that assesses pain perception in the central nervous system (97). In the tail flick test, which assess the spinal reflex to painful stimuli, the tolerance is reduced in β-Arr2 KO mice (92). Replacing a portion of the cytoplasmic tail of the MOR with the corresponding sequence from the δ-opioid receptor increases MOR internalization and reduces the tolerance to morphine (98). Following chronic morphine treatment, compensatory changes are classically observed: upregulation of adenylyl cyclases and other components of the cAMP pathway including CREB and delta FosB. Such compensatory mechanisms are not modified in β-Arr2 KO mice (97). Physical symptoms of morphine dependency are also unmodified in these mice. Curiously, some morphine-induced responses such as constipation, respiratory suppression, and hyperlocomotor activity are diminished in β-Arr2 KO mice (92). Thus, the latter effects may in part be mediated by a G protein-independent β-Arr2 signaling pathway. However, other explanations are possible.

Deletion of the *spinophilin* gene causes phenotypes that are almost opposite to those obtained following deletion of β-Arr2 (95). These include an increase in adenylyl cyclase inhibition by morphine, an increase in endocytosis and recycling of MOR, and a decrease in morphine-induced ERK activation. At the behavioral level, deletion of the *spinophilin* gene reduces analgesic effects of acute morphine treatment but enhances adaptations to repeated morphine exposure, including an increase in analgesic tolerance, dependency (exacerbated withdrawal), and place conditioning (95). All these phenotypes mimic features of addiction. In conclusion, spinophilin seems to reduce the long-term negative effects of repeated opiate exposure and represents a potential target for the treatment of opiate addiction.

5-HT_{2C} RECEPTOR-GIP INTERACTIONS: NEW TARGETS FOR THE TREATMENT OF ADDICTION AND MOOD DISORDERS?

Among the GPCRs activated by serotonin (5-hydroxytryptamine, 5-HT), the 5-HT_{2C} receptor is of particular interest in view of its broad physiological role and implication in the actions of numerous psychoactive drugs (99–101). For instance, the 5-HT_{2C} receptor is the 5-HT receptor that is most clearly associated with effects of drugs of abuse, including sensitization, conditioned place preference, and drug self-administration (102). The rewarding effects of these drugs are strongly related to an increase in the firing rate of ventral tegmental area (VTA) dopaminergic neurons innervating the NAc, which are tonically inhibited under normal conditions via 5-HT_{2C} receptor-mediated activation of GABAergic interneurons. The 5-HT_{2C} receptor also plays an essential role in the regulation of mood, and alteration of its functional activity has been implicated in the etiology of anxio-depressive states (100). The 5-HT_{2C} receptor is itself the target of various classes of antidepressants, which induce antagonistic effects (103). Antidepressant action

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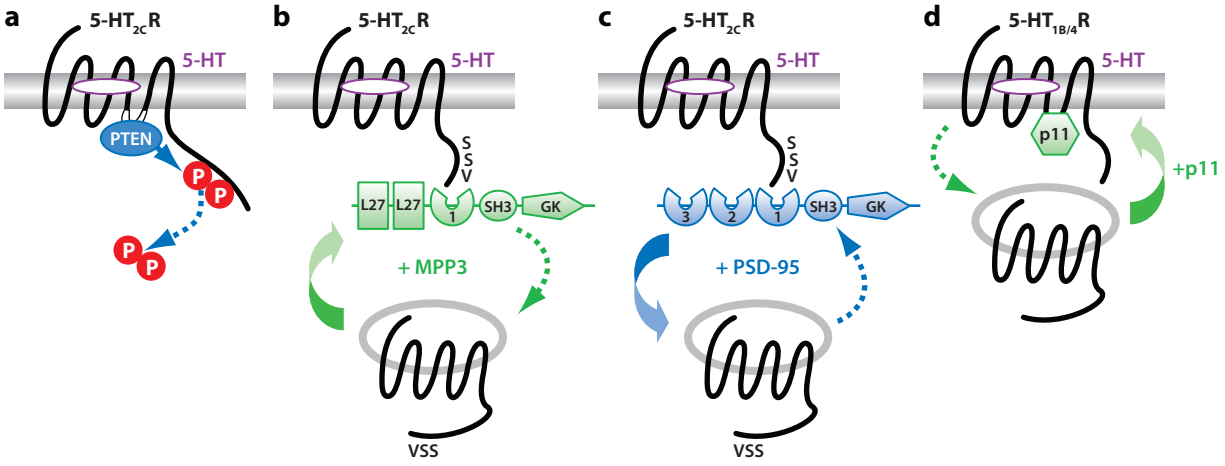

Figure 3

Interaction of 5-HT receptors with GIPs: modulation of receptor phosphorylation state and plasma membrane localization. (*a*) PTEN associated with the third intracellular loop of the 5-HT_{2C} receptor induces receptor dephosphorylation and thereby reinforces the effects of drugs of abuse. (*b*,*c*) Interaction of the 5-HT_{2C} receptor with the PDZ domain-containing proteins MPP3 and PSD-95 differentially modulate receptor desensitization and trafficking: PSD-95 increases desensitization of the receptor-operated Ca^{2+} response as well as constitutive and agonist-induced receptor internalization, whereas MPP3 stabilizes the receptor at the plasma membrane and prevents receptor desensitization. (*d*) P11 binds to the third intracellular loop of presynaptic 5-HT_{1B} receptors and postsynaptic 5-HT_4 receptors, inducing an increase in their plasma membrane localization.

of 5-HT_{2C} antagonists has been attributed to activation of the mesocorticolimbic dopaminergic pathway, which exerts a favorable influence upon mood (100).

The 5-HT_{2C} receptor is one of the GPCRs for which the largest number of GIPs has been identified. Some of them are critical for its functional activity (104). PTEN (protein phosphatase and tensin homolog) directly associates with the third intracellular loop of the receptor, preventing agonist-induced receptor phosphorylation in PC12 cells (**Figure 3*a***) (105). Disruption of receptor/PTEN complexes with a cell-penetrating peptidyl mimetic of the PTEN-binding motif (Tat-3L4F) inhibits PTEN-induced receptor dephosphorylation. PTEN also influences receptor activity in vivo. Intravenous delivery of the Tat-3L4F peptide in rats disrupts PTEN/5-HT_{2C} receptor complexes in the VTA and decreases the firing rate of VTA dopaminergic neurons. The peptide also prevents Δ9-tetrahydrocannabinol (THC)-induced increase in firing rate of these neurons, thereby reproducing the effect of 5-HT_{2C} receptor agonists. As 5-HT_{2C} receptor agonists, this peptide also inhibits the rewarding effects of THC (and nicotine) mediated by VTA dopaminergic neurons. However, it does not reproduce the side effects (e.g., anxiety, penile erection, hypophagia, and suppression of locomotor activity) observed following administration of 5-HT_{2C} agonists. These experiments suggest that targeting the interaction between 5-HT_{2C} receptor and PTEN might be an effective strategy for the treatment of addiction-related behaviors, with perhaps less pronounced side effects than occur with strategies that involve the use of 5-HT_{2C} agonists.

The 5-HT_{2C} receptor also interacts with several PDZ proteins (106, 107), which might be important for addiction-related phenotypes. *Mpdz*, a gene encoding one of the receptor PDZ partners, multiple PDZ protein 1 (MUPP1) (106, 108), has been identified as a quantitative trait that underlies physical dependency of drugs of abuse and its modulation by 5-HT_{2C} receptor (109). However, MUPP1 interacts with numerous proteins, and additional receptor-operated signaling might also be involved in its effects related to drug dependency.

Protein phosphatase and tensin homolog (PTEN): a tumor suppressor that exhibits both lipid (PIP3) and protein phosphatase activities

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P11: a Ca^{2+}-insensitive member of the S100 protein superfamily that binds to 5-HT_{1B}, 5-HT_{1D}, and 5-HT_4 receptors, and enhances their signaling efficiency

Association of 5-HT_{2C} receptors with PDZ proteins affects both receptor desensitization and internalization (110, 111). Interestingly, the effects depend on the nature of the PDZ protein associated with the receptor (111). For instance, association of the receptor with PSD-95 increases receptor desensitization and internalization, whereas its association with MAGUK p55 subfamily member 3 (MPP3) prevents receptor internalization (**Figures 3*b*** and ***c***). These opposite actions highlight the importance of identifying which PDZ protein is associated with the receptor at a given time within a given neuron in native brain tissue. In any case, disruption of 5-HT_{2C} receptor-PDZ protein complexes by a cell penetrating and interfering peptide increases receptor desensitization in cortical neurons, indicating that interaction of 5-HT_{2C} receptors with PDZ proteins prevents receptor desensitization (111). Several lines of evidence indicate that full therapeutic activity of antidepressants, such as specific reuptake inhibitors, depends on the desensitization and/or downregulation of various 5-HT receptors. These include not only 5-HT_{1A} autoreceptors, but also 5-HT_{2C} receptors, which, as mentioned above, exert a negative influence upon mood (99). Targeting 5-HT_{2C} receptor-PDZ protein interactions to increase receptor desensitization might therefore constitute an attractive strategy to develop new drugs that may improve the therapeutic efficacy of antidepressants.

INTERACTION OF P11 WITH 5-HT_{1B} AND 5-HT_4 RECEPTORS, A CRUCIAL EVENT IN ANTIDEPRESSANT ACTION

P11 (also called S100A10 or calpactin 1 light chain or annexin 2 light chain) is an inducible 97-amino acid protein member of the S100 superfamily comprising 10–14 kDa, EF hand-containing Ca^{2+}-binding proteins, which transmit Ca^{2+}-dependent cell-regulatory signals. These proteins are present in a large number of organisms, including vertebrates, invertebrates, and plants (112). P11 differs from other members of the S100 family by its Ca^{2+} insensitivity. P11 forms heteromers with the trafficking protein annexin 2 (112) and several GPCRs activated by 5-HT implicated in mood disorders and antidepressant actions. These include the 5-HT_{1B} and 5-HT_{1D} receptors, two closely related receptors expressed in nerve terminals of 5-HT, dopaminergic, GABAergic, and glutamatergic neurons (113, 114). 5-$HT_{1B/1D}$ receptors are negatively coupled to adenylyl cyclase and inhibit neuronal firing. P11 also binds to the postsynaptic 5-HT_4 receptor, which does not share sequence homology with 5-$HT_{1B/D}$ receptors and is positively coupled to adenylyl cyclase via $G\alpha_s$ (114). Note that p11 does not interact with the 5-HT_6 receptor, another $G\alpha_s$-coupled 5-HT receptor implicated in antidepressant action, suggesting that interactions between p11 and 5-HT receptors are highly specific. Studies performed in cell lines indicate that interaction of p11 with both 5-HT_{1B} and 5-HT_4 receptors increases their localization at the cell surface and, correspondingly, enhances their signal transduction efficacy (**Figure 3*d***). In line with these observations, alteration of 5-HT_{1B} and 5-HT_4 receptor-operated signaling was observed in brain tissue and/or primary cultured neurons from p11 KO mice (113, 114).

The identification of p11 as a 5-HT_{1B} receptor-binding partner prompted further investigation on the role of this protein in the regulation of mood disorders (113). A first series of experiments suggested that altered p11-mediated regulation of 5-HT_{1B} receptor function might be involved in depressive states: (*a*) the level of p11 is reduced in a genetic animal model of depression (115), as well as in the brain of patients with unipolar major depression; (*b*) treatment with the tricyclic imipramine or electroconvulsive therapy in the mouse increases cortical expression of the protein, and transgenic mice overexpressing p11 in neurons exhibit behavioral features reminiscent of those observed after antidepressant treatment; and (*c*) both a depression-like syndrome and reduced responsiveness to 5-HT_{1B} receptor agonists and imipramine are observed in p11 KO mice (113). Moreover, these mice are resistant to antidepressant and anxiolytic effects induced

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by administration of the selective 5-HT_4 receptor agonist RS67333, suggesting that interaction between p11 and the 5-HT_4 receptor might contribute to behavioral responses to receptor stimulation (114). Consistent with the lack of association of p11 with the 5-HT_6 receptor, the antidepressant effect of 5-HT_6 receptor stimulation is not affected in p11 KO mice. Collectively, these data underscore the central role of p11 interactions with 5-HT_4 and 5-HT_{1B} receptors in vulnerability to depression and in the response to various classes of antidepressants. However, the relative contribution of p11–5-HT_{1B} versus p11–5-HT_4 receptor complexes in antidepressant activity remains to be elucidated.

Interaction between p11 and 5-HT_{1B} receptors might also be involved in the response of Parkinson's disease patients to L-DOPA treatment. Chronic L-DOPA administration in a unilateral 6-OHDA-lesioning animal model of the disease induces expression of both 5-HT_{1B} receptors and p11 in dopamine-denervated striatonigral neurons, an effect mediated by activation of D_1 receptors (116). Co-administration of a 5-HT_{1B} agonist (CP93139) reduces L-DOPA-induced abnormal involuntary movements by inhibiting a D_1 receptor-mediated increase in GABA release from striatonigral neurons in wild-type mice. In contrast, CP93139 does not affect L-DOPA motor activity in p11 KO mice, suggesting again that 5-HT_{1B} receptor-mediated effects largely depend on association of the receptor with p11. As serotonergic innervation of the striatum is relatively preserved in Parkinson's disease, it has been proposed that joint induction of 5-HT_{1B} receptors and p11 upon chronic L-DOPA administration might serve as a negative feedback mechanism that counteracts hyperactivity of striatonigral neurons, thereby reducing abnormal movements in L-DOPA-treated patients (116).

PATHOLOGIES ASSOCIATED WITH OPSIN AND OTHER GPCR MIS-LOCALIZATION

In many specialized cells such as neurons and mammalian photoreceptors, GPCRs in primary cilia must reach their destination far from peri-nuclear Golgi where they are synthesized. This requires a long range of intracellular transport because of the large size and/or idiosyncratic geometry of these cells. Furthermore, neurons are polarized cells composed of two functionally separated compartments: the somato-dendritic and the axonal compartment. How GPCRs are sorted and transported to either one of these subcellular compartments is poorly understood. Such sorting and transport probably depend on specific domains of the receptors and of their associated GIPs, as well as the type of neuron in which sorting and transport occur. Some examples have been mentioned above. Another important one within the nervous system is photoreceptors, among which the transport of opsin has been studied in detail. The extreme C-terminus of opsin (Gln344-VAPA) is highly conserved among vertebrates and is a hotspot for mutations that cause retinitis pigmentosa (117). Two of these C-terminus mutants (Gln344-ter and Pro347-Leu) are characterized by a specific defect in rhodopsin transport due to a defective transport of ospin to the plasma membrane of the connecting cilium (117). Once present at the plasma membrane of the connecting cilium, opsin binds to the kinesin-II microtubule motor KIF3A and is transported to the outer segment. KIF3A is also required for the targeting of β-Arr to the outer segment (118). More surprising is the observation that KIF3A also targets smoothened (Smo), an atypical GPCR, and β-Arr to the primary cilium (119). The Smo-β-Arr-KIF3A complex is crucial for promoting synthesis of GliA, a transcription factor that acts downstream of Smo signaling (119).

The Bardet-Biedl syndrome (BBS) is characterized by pathologies ranging from cystic kidney disease to brain malformations, cognitive deficits, obesity, and retinal dystrophy. Members (Bbs2 and Bbs4) of the protein family implicated in this syndrome are necessary for the ciliary localization

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of somatostatin and melanin-concentrating hormone receptors (120). However, whether or not these proteins are GIPs is unknown.

CONCLUSION AND FUTURE PERSPECTIVES

Like many biological functions that are carried out by multiprotein complexes, modulation of neuronal activity by GPCR ligands critically depends on the association of certain GPCRs with GIPs. An increasing number of neurological and psychiatric disorders have been found to result from an alteration of GPCR-GIP interactions, which thereby offer attractive opportunities for therapeutic intervention. The proof of concept has been established for several pathologies by means of cell-penetrating peptidyl tools. The next step will almost certainly be the development of small-molecule inhibitors or allosteric modulators of protein-protein interactions instead of peptides. The lack of small natural molecules binding to protein-protein interfaces as starting points for drug design, as well as the necessity to find drugs that specifically affect interactions between a given GPCR-GIP pair, remain important challenges in this task. Several recent success stories in other systems (121) suggest that such a strategy may be possible.

SUMMARY POINTS

1. GPCRs associate with a large number of soluble proteins called GIPs that are often assembled into large multiprotein complexes. These complexes are involved in the fine-tuning of signal transduction properties of GPCRs. The roles of GIPs in CNS physiology and pathologies have recently emerged.
2. Homer-mGluR interactions, which have a major role in synaptic plasticity, have been involved in Fragile X mental retardation, schizophrenia, anxiety, attention deficit, and neuroplasticity associated with acute and chronic action of drugs of abuse such as cocaine and alcohol. Homer-mGluR interactions might also contribute to the reduction of neuronal excitability, especially during epileptic seizure and inflammatory pain.
3. PICK1 interacts with mGluR7 and many other synaptic proteins. PICK1/mGluR7 complexes are required for the inhibition of presynaptic P/Q channels by mGluR7 agonists. Disrupting PICK1-mGluR7 interaction in vivo induces absence epilepsy.
4. Dopamine D_2 receptors form a complex with β-arrestin, phosphatase 2A, and Akt. This complex regulates GSK3 signaling and is implicated in behavioral effects of dopamine, amphetamine, antipsychotics, and antidepressants including lithium.
5. β-arrestins and spinophilins have an opposite role in adverse effects (including tolerance, dependency, and addiction) associated with the chronic use of opiates.
6. Interactions of several 5-HT receptor subtypes (5-HT_{1B}, 5-HT_{2C}, and 5-HT_4 receptors) with GIPs have been implicated in addiction and mood disorders, thereby identifying new therapeutic targets for the treatment of such psychiatric diseases.

FUTURE ISSUES

1. It is likely that the full spectrum of GIPs is not yet known. Newly discovered GIPs might provide molecular cues for understanding the mechanisms of trafficking, targeting, and signaling of many, perhaps most, GPCRs.

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2. Several GIPs display competitive interactions for a given GPCR, which can specify receptor signaling. This is the case for monomeric versus multimeric Homer interaction with mGluR1a/5, and for PSD-95 versus MPP3 association with the 5-HT_{2C} receptor. Therefore, a major issue will be to clarify the kinetics and detailed mechanisms (including their possible analysis by crystallography or other techniques) of these competitive interactions.
3. Theoretically, any functional alteration of GIP interaction might represent a potential source of pathological disorder and, therefore, might be a therapeutic target. Nevertheless, some GIP dysfunctions may be naturally compensated by physiological mechanisms, minimizing their therapeutic impact. It is also possible that transient disruption of a GIP interaction represents a protective mechanism per se, as illustrated by the antiepileptic effect of disrupting Homer interactions by the immediate early gene *Homer1a*. Therefore, a major issue will be to further characterize the implication of GIPs in neuropathologies and to validate them as valuable therapeutic targets.
4. A final issue will be to modulate GIP interactions as a means to compensate for effects observed in neurological and psychiatric disorders. This will require the development of peptidic and nonpeptidic compounds able to antagonize or facilitate GIP interactions. The most challenging issue for this task will be to understand the structural determinants that underlie the specificity of these interactions, in order to generate sufficiently selective compounds that maximize efficacy and minimize toxicity.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

C.B., J.B., L.F., P.M., and J.P. were supported by grants from CNRS, INSERM, the French Minister of Research (contracts ANR-05-NEUR-035-01, ANR-08-MNP-034, ANR-08-MNPS-011, ANR-08-MNPS-026, and ANR-08-MNPS-037), and the region Languedoc-Roussillon. C.B., J.B. and P.M. were also supported by grants from Servier Pharmaceuticals, C.B. and P.M. by the French Foundation for Medical Research (FRM Team 2005), and L.F. by a grant from the European Community (Health-F2-2008-222918).

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Shows that disruption of mGluR5-Homer interaction blocks mGluR5-induced LTD and its translational activation. These effects are lost in Fmr1 KO mice.

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Shows that a 50% reduction of mGluR5 expression in mouse brain brings multiple and varied fragile X phenotypes closer to normal background.

Provides evidence of the role of Homer in cocaine addiction.

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Annual Review of Pharmacology and Toxicology

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