of transporters and receptors, the flat, expansive, and adaptive topology of the protein–protein interface presents a sizeable challenge to the goal of identifying small molecules that result in a gain or loss of function of the protein complex. This is offset by the growing body of evidence to suggest that a few amino acids at the interface ('hot spot') contribute to the majority of the binding energy in protein–protein interactions suggesting that modulators with a high degree of specificity could be developed. Furthermore, recent advances in screening technologies and accessibility to an ever-increasing diversity of small molecules suggest that protein–protein interactions are a viable option for drug discovery (Simeonov *et al*, 2008; Wells and McClendon, 2007).

Much of the groundwork to suggest that targeting 'hot-spots' could result in either loss or gain of cellular function is found in the cancer field (Simeonov *et al*, 2008; Wells and McClendon, 2007). For example, the interaction between the C-terminal domain of the breast cancer gene 1 (early onset; BRCA1) protein and BRCA1-associated carboxyl terminal helicase (BACH1) protein is essential for DNA damage-induced checkpoint control. A competitive, high-throughput assay has allowed the identification of small molecule BRCA1-BACH1 inhibitors, which are currently being validated in cell-based assays and ultimately in preclinical studies to improve the efficacy of breast and ovarian cancer therapeutics (Simeonov *et al*, 2008).

Protein–protein interactions also hold promise as a target for medications development in neurology and psychiatry. Bertaso *et al* (2008) found that uncoupling of the metabotropic glutamate receptor 7a (mGluR7a) from protein interacting with kinase 1 (PICK1) is sufficient to induce absence seizures in rodents. A small molecule enhancer of this protein–protein interaction would be predicted to provide therapeutic potential for epilepsy. Therapeutic potential also may exist in the disruption of protein–protein interactions with the serotonin 5-HT_{2C} receptor (5-HT_{2C}R), an important protein in normal and abnormal psychiatric states (Bubar and Cunningham 2008). The 5-HT_{2C}R interacting protein multiple PDZ (MPDZ) domain protein encodes the first *bona fide* quantitative trait gene underlying physical dependence to abused drugs (Shirley *et al*, 2004). A small molecule inhibitor of the 5-HT_{2C}R-MPDZ interaction could alter downstream signaling associated with this receptor. Small peptide inhibitors of the 5-HT_{2C}R-MPDZ interaction have been developed (Sharma *et al*, 2007) but have yet to be tested for their ability to alter addiction-(or psychiatric-)relevant phenotypes. Thus, 5-HT_{2C}R protein–protein interactions represent a fruitful ground for the rational development of small molecular inhibitors to treat psychiatric illnesses.

A third example is the intracellular scaffolding protein Homer. Homer proteins form a network, which brings together key signaling molecules at the postsynaptic density (eg, mGluR5 and NMDA receptors) to regulate intracellular calcium cascades. Homer-2 expression critically regulates the responses to cocaine and alcohol (Szumlinski *et al*, 2008) probably through disruption of protein–protein interactions in which it participates. The design of small molecule inhibitors of Homer protein–protein interactions also holds promise for novel pharmacotherapies in psychiatry.

We are just beginning to appreciate the relationship between protein–protein interactions and neuronal function. Targeting protein–protein interactions has great therapeutic potential as noted in the above examples. Making these interactions 'druggable' is a critical challenge in the development of new treatments for psychiatric and neurological disorders. Thus, mining protein–protein interactions is opening the way for a paradigm shift in drug discovery efforts to identify new therapeutics for neurological and psychiatric disorders.

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DISCLOSURE/CONFLICT OF INTEREST

The authors declare that except for income received from their primary employers, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional services, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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Neuropsychopharmacology Reviews (2009) **34,** 247–248; doi:10.1038/npp.2008.167

Promise of mGluR2/3 activators in psychiatry

The group II metabotropic glutamate receptors (mGluRs), mGluR2 and mGluR3, have emerged as exciting and well-validated targets for novel therapeutic agents used for treating psychiatric disorders. A large number of preclinical and clinical studies provide strong evidence that mGluR2/3 agonists may provide a novel approach to treatment of anxiety disorders and

schizophrenia. Group II mGluR agonists, such as LY354740 and related compounds, have robust activity in a range of animal models that predict anxiolytic (Swanson *et al*, 2005) and antipsychotic (Schoepp and Marek, 2002) activities. Furthermore, clinical studies reveal that group II mGluR agonists have robust efficacy in human models of panic attack and fear-potentiated startle (Swanson *et al*, 2005) and improve ratings for positive and negative symptoms in patients suffering from schizophrenia (Patil *et al*, 2007). In these trials, there were no major liabilities associated with current medications, including sedation, amnesic symptoms, withdrawal upon discontinuation of the drug, prolactin elevation, extrapyramidal symptoms, or weight gain.

These exciting clinical findings represent a major breakthrough and could ultimately lead to the introduction of mGluR2/3 activators as a novel approach to treatment of anxiety disorders and/or schizophrenia. However, it is not yet clear whether orthosteric agonists of these receptors will reach the market for broad clinical use. Also, these agonists activate both mGluR2 and mGluR3 and do not provide insights into which of these group II mGluR subtypes is most important for the clinical efficacy. Recently, a novel class of compounds, known as positive allosteric modulators (PAMs), that are selective for mGluR2 have shown exciting potential as an alternative approach to mGluR2/3 agonists. Unlike the mGluR2/3 agonists, these compounds do not activate mGluR2 directly but bind to a site distinct from the glutamate-binding site to increase responses of mGluR2 to glutamate. Multiple mGluR2 PAMs have been identified, all of which are structurally related to two prototypical mGluR2 PAMs, termed LY487379 (Johnson *et al*, 2003; Galici *et al*, 2005) and BINA (Galici *et al*, 2006). These compounds are highly selective for mGluR2 relative to mGluR3 or any other mGluR subtype and have robust effects in potentiating responses to group II mGluR agonists at several glutamatergic synapses (Johnson *et al*, 2003; Galici *et al*, 2006). Interestingly, psychomimetic agents increase activity of glutamatergic synapses in the prefrontal cortex (PFC) and this has been postulated to be critical in the pathophysiology of schizophrenia. Effects of psychomimetic agents on glutamatergic transmission in the PFC are blocked by group II mGluR agonists and by the mGluR2 PAMs. Furthermore, multiple structurally distinct mGluR2-selective PAMs have efficacy in animal models that predict both antipsychotic (Galici *et al*, 2005 , 2006) and anxiolytic (Johnson *et al*, 2003; Galici *et al*, 2005) activities, which are very similar to those observed with the mGluR2/3 orthosteric agonists. These studies raise the exciting possibility that selective mGluR2 PAMs may provide a novel approach to treatment of schizophrenia and anxiety disorders that could be devoid of the adverse effects associated with currently available drugs.

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DISCLOSURE/CONFLICT OF INTEREST

Dr Conn has received compensation over the past 2 years as a consultant from Merck and Co, Johnson and Johnson, Hoffman La Roche, GlaxoSmithKline, Lundbeck Research USA, Epix Pharmaceuticals, Invitrogen Life Technologies, Evotec Inc., Addex Pharmaceuticals, Michael J Fox Foundation, Seaside Therapeutics, Cephalon Inc., AstraZeneca USA, NeurOp Inc., Forest Research Institute, LEK Consulting, The Frankel Group, Prestwick Chemical Co, Millipore Corp., Genentech, IMS Health, Primary Insight, and Otsuka.

Dr Conn has received honoraria as a speaker from University of Toronto, American Society for Bone and Mineral Research, University of Alabama Birmingham, University of Michigan, Southern Research Institute, Harvard Medical School, and the University of North Carolina.

Dr Conn receives research support that includes salary support from NIH, Michael J Fox Foundation, Seaside Therapeutics, and Vanderbilt University.

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Neuropsychopharmacology Reviews (2009) **34,** 248–249; doi:10.1038/npp.2008.156

Targeting AMPA and kainate receptors in neurological disease: therapies on the horizon?

Aberrant excitatory neurotransmission is a prominent pathological component in many neurological and psychiatric diseases. Not surprisingly, the proteins that mediate the majority of excitatory signaling, ionotropic glutamate receptors (iGluRs), represent tempting targets for drug development efforts. This potential remains largely unrealized, however, despite a wealth of promising preclinical data. Here I discuss briefly the new applications and candidate drugs acting on the AMPA and kainate subtypes of iGluRs that suggest that a renaissance might be underway.

AMPA and kainate receptors subserve different roles in the brain. AMPA receptors mediate the majority of fast excitatory neurotransmission and are critical cellular constituents of learning and memory processes. Overactivation of AMPA receptors, however, can be damaging to the nervous system, producing convulsions or neuronal death. Kainate receptors play