Published in final edited form as:
Neuropsychopharmacology. 2009 January ; 34(1): 248–249. doi:10.1038/npp.2008.156.

Promise of mGluR2/3 activators in psychiatry

P Jeffrey Conn[1] and **Carrie K Jones**[1]

P Jeffrey Conn: jeff.conn@vanderbilt.edu

[1] Vanderbilt Program in Drug Discovery, Department of Pharmacology, Vanderbilt Medical Center, Nashville, TN, USA

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

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.

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.

Acknowledgments

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

References

Galici R, Echemendia NG, Rodriguez AL, Conn PJ. A selective allosteric potentiator of metabotropic glutamate (mGlu) 2 receptors has effects similar to an orthosteric mGlu2/3 receptor agonist in mouse models predictive of antipsychotic activity. J Pharmacol Exp Ther 2005;315:1181–1187. [PubMed: 16123306]

Galici R, Jones CK, Hemstapat K, Nong Y, Eche- mendia NG, Williams LC, et al. Biphenyl- indanone A, a positive allosteric modulator of the metabotropic glutamate receptor subtype 2, has antipsychotic- and anxiolytic-like effects in mice. J Pharmacol Exp Ther 2006;318:173–185. [PubMed: 16608916]

Johnson MP, Baez M, Jagdmann GE Jr, Britton TC, Large TH, Callagaro DO, et al. Discovery of allosteric potentiators for the metabotropic glutamate 2 receptor: synthesis and subtype selectivity of N-(4-(2-methoxyphenoxy)phenyl)-N-(2,2,2- trifluoroethylsulfonyl)pyrid-3-ylmethylamine. J Med Chem 2003;46:3189–3192. [PubMed: 12852748]

Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, et al. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. Nat Med 2007;13:1102–1107. [PubMed: 17767166]

Schoepp DD, Marek GJ. Preclinical pharmacology of mGlu2/3 receptor agonists: novel agents for schizophrenia? Curr Drug Target CNS Neurol Disord 2002;1:215–225.

Swanson CJ, Bures M, Johnson MP, Linden AM, Monn JA, Schoepp DD. Metabotropic glutamate receptors as novel targets for anxiety and stress disorders. Nat Rev Drug Discov 2005;4:131–144. [PubMed: 15665858]