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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Galici R, Echemendia NG, Rodriguez AL, Conn PJ (2005). 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* **315**: 1181–1187.

Galici R, Jones CK, Hemstapat K, Nong Y, Echemendia NG, Williams LC *et al* (2006). Biphenylindanone A, a positive allosteric modulator of the metabotropic glutamate receptor subtype 2, has antipsychotic- and anxiolytic-like effects in mice. *J Pharmacol Exp Ther* **318**: 173–185.

Johnson MP, Baez M, Jagdmann Jr GE, Britton TC, Large TH, Callagaro DO *et al* (2003). 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* **46**: 3189–3192.

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

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

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

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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

more modulatory roles, fine-tuning the balance between neuronal excitation and inhibition.

Positive AMPA receptor modulators strengthen excitatory transmission, enhance synaptic plasticity, and preclinical and preliminary clinical research suggested efficacy as cognition enhancers (Lynch, 2006; O'Neill and Dix, 2007). The first potentiator tested in large clinical trials was CX516 (Cortex Pharmaceuticals), which did not show efficacy in a variety of pathologies (eg Berry-Kravis *et al*, 2006). In contrast, a second-generation ampakine, CX717, normalized behaviors associated with attention deficit hyperactivity disorder (ADHD). Further testing of CX717 for ADHD was not approved by the US Food and Drug Administration due to toxicological concerns, although approval was granted to continue trials of CX717 in Alzheimer's disease. The outcome of this project is uncertain, however, given that a chemically distinct potentiator, LY415395 (Eli Lilly), failed to improve cognitive performance in an Alzheimer's disease trial (Chappell *et al*, 2007). Recently, compelling preclinical data prompted initiation of two Phase II trials in Germany to determine if CX717 reverses or prevents respiratory depression during opiate analgesia. These appear to be the only ongoing studies of efficacy for positive AMPA receptor modulators in humans, as clinical studies for similar molecules have been suspended (Schering-Plough) or the results remain undisclosed (Servier, GlaxoSmithKline).

Noncompetitive inhibitors of AMPA receptors, such as talampanel (Teva Pharmaceuticals) and perampanel (Eisai Medical Research), reduce overexcitation and potentially slow neurodegeneration. These drugs were efficacious as adjunct therapies for refractory partial complex seizures (Howes and Bell, 2007); perampanel also alleviated diabetic and postherpetic neuropathic pain and will be further tested for these indications. Results released from an in-progress study suggested that talampanel decreased mortality from glioblastoma, and an examination of its efficacy in amyotrophic lateral sclerosis is planned. Perampanel was not effective as an add-on therapy to levodopa in Parkinson's disease, however, and this program was terminated by Eisai.

Preclinical data suggest that kainate receptors represent an untapped and attractive target for drug development. A nonselective AMPA/kainate receptor inhibitor, tezampanel (NGX424; Torrey Pines Pharmaceutics), reduced both migraine pain and other symptoms in a recent Phase II trial. This clinical efficacy is likely attributable to inhibition of kainate receptors, based on preclinical evidence with more selective antagonists developed by Eli Lilly. A chemically distinct AMPA/kainate receptor antagonist, NS1209 (NeuroSearch A/S), also alleviated refractory status epilepticus and neuropathic pain in small Phase II studies, but further research into this molecule was suspended. The apparent success of the first representatives of this new class of drugs provides a strong impetus for further development and clinical testing.

It is evident from this overview that there is reason for both optimism and healthy skepticism regarding the clinical prospects of drugs targeting AMPA and kainate receptors. Cusp of a renaissance or a false dawn? Perhaps a Magic 8-Ball offers the best advice for would-be prognosticators: 'Ask again later.'

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Berry-Kravis E, Krause SE, Block SS, Guter S, Wuu J, Leurgans S *et al* (2006). Effect of CX516, an AMPA-modulating compound, on cognition and behavior in fragile X syndrome: a controlled trial. *J Child Adolesc Psychopharmacol* **16**: 525–540.

Chappell AS, Gonzales C, Williams J, Witte MM, Mohs RC, Sperling R (2007). AMPA potentiator treatment of cognitive deficits in Alzheimer disease. *Neurology* **68**: 1008–1012.

Howes JF, Bell C (2007). Talampanel. *Neurotherapeutics* **4**: 126–129.

Lynch G (2006). Glutamate-based therapeutic approaches: ampakines. *Curr Opin Pharmacol* **6**: 82–88.

O'Neill MJ, Dix S (2007). AMPA receptor potentiators as cognitive enhancers. *IDrugs* **10**: 185–192.

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Gene expression profiling in blood: new diagnostics in alcoholism and addiction?

The successful treatment of most diseases relies heavily upon early detection. Biomarkers with diagnostic and prognostic value are critical to the addiction field. Most individuals with alcohol or drug dependence or use problems evade detection until severe medical, legal, or social consequences arise. The short half-life of alcohol in the blood after cessation of drinking eliminates the feasibility for using blood alcohol as a biomarker. Carbohydrate-deficient transferrin (CDT) is currently the most specific serum marker of chronic, heavy alcohol use (Reynaud *et al*, 2000), but the low sensitivity of the CDT test in the general population makes it an unreliable candidate for predicting either heavy alcohol use or for diagnosing alcohol abuse and/or dependence (Alte *et al*, 2004). Except for the drugs and their metabolites, there are not biomarkers for addiction.

Advances in the field of genomics offer new diagnostic and screening potential for complex genetic diseases like addiction. The ability to simultaneously measure the level of all possible transcripts (mRNAs) provides an unbiased view of potential biomarkers. The importance of understanding gene expression changes in alcohol and drug dependence can be appreciated by the impact of expression profiling in other diseases, most notably cancer, where studies have led to improved pharmacotherapies and to a molecular classification of disease. Gene expression profiling is only beginning to be applied to psychiatric