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Commentary

mGluR2-Positive Allosteric Modulators: Therapeutic Potential for Treating Cocaine Abuse?

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The heterogeneous distribution of the metabotropic glutamate receptors (mGluRs) in the mammalian brain and the variety of receptor subtypes potentially regulating a range of neuropharmacological activities have long been attractive targets for the development of compounds that selectively interact with the eight identified receptor subtypes. Over the past several years, a large number of studies have suggested a potential role for mGluRs in a variety of psychiatric and neurological disorders ranging from depression, anxiety, and schizophrenia to pain, Alzheimer's, and Parkinson's disease. Group II mGlu receptors, which include the mGluR2 and 3 receptor subtypes, have been the focus for anxiolytic and antipsychotic activity, with mGluR2/3 receptor agonists showing efficacy in early clinical studies for treatment of these conditions (Swanson *et al*, 2005; Patil *et al*, 2007). Until recently, it was not possible to delineate which of these two receptor subtypes were responsible for these effects. However, with the introduction of highly selective mGluR2 agonists (eg, Johnson *et al*, 2003) known as positive allosteric modulators (PAMs), it has become possible to delineate the potential therapeutic relevance of this receptor (Marino and Conn, 2006). In contrast to the dual-acting mGluR2/3 agonists, the mGluR2 PAMs do not activate the receptor directly but bind to a site that is distinct from the glutamate-binding site to potentiate glutamate-induced activation of the receptor. A limitation of these early compounds, however, has been their relatively modest *in vivo* potencies and short duration of action, which has hindered a detailed examination of their pharmacological actions.

It is with this background that one of these relatively recently identified selective mGluR2 PAMs, 3′-([(2-cyclopentyl-6, 7-dimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yl)oxy)methyl) biphenyl-4-carboxylic acid, designated as biphenylindanone A (BINA), a compound with more favorable pharmaceutical properties than those previously identified (Galici *et al*, 2006), has been studied by Jin *et al* (2010). BINA was compared with the mGluR2/3 agonist LY379268 ((−)-4-aminobicyclo(3.1.0)hexane-4,6-dicarboxylic acid)) in a number of preclinical models relevant to cocaine abuse. The results of these studies are reported in this issue of *Neuropsychopharmacology*. BINA is a potent and highly selective potentiator of the response of mGluR2 to glutamate and has no effect on other mGluR receptor subtypes. Furthermore, in contrast to other mGluR PAMS, its effects are long lasting and robust, making it a more suitable compound with which to explore its behavioral and pharmacological actions. The studies reported by Jin *et al* (2010) build impressively upon the extensive literature implicating the role of glutamate in substance abuse, and effectively capture the impressive systematic progression of efforts within the pharmaceutical industry and now in academic centers to develop selective compounds that can be used to explore potential therapeutic benefits in appropriate animal model systems.

Jin *et al* (2010) examined the effects of BINA and LY379268 on cocaine self-administration in rats having short (1 h) or long (6 h) access to cocaine. In addition, these two compounds were also examined with food as the maintaining event in an effort to determine whether the effects of these compounds were specific to either reinforcer. This assessment is important as a means of determining whether a compound might produce a non-selective increase or decrease in behavior, irrespective of the type of maintaining event. The effects of extinction were studied, followed by a reinstatement procedure in which the stimulus that was previously correlated with either cocaine or food delivery was presented to determine whether this stimulus would reinstate responding for either cocaine or food and whether BINA would affect the stimulus-induced reinstatement. Jin *et al* (2010) also examined the effects of BINA on intracranial self-stimulation reward thresholds under both baseline and during cocaine-induced enhancement. Finally, in an effort to more completely characterize the effects and pharmaceutical properties of BINA, these investigators incorporated novel *in vitro* assays to show mGluR2 PAM selectivity and functional activity; they also determined the pharmacokinetic properties and blood–brain barrier penetration of this compound. This combination of assays and evaluations, spanning the spectrum of

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in vitro and *in vivo* assays, both characterizing and profiling the compound for its pharmacological, pharmaceutical, and behavioral activities is impressive in its scope, reassuring in its outcome, and provides a compelling testimony to the benefits of collaborative academic science coupled to drug discovery efforts.

The results comparing BINA with LY379268 on cocaine self-administration are quite striking, with BINA (10–40 mg/kg) producing a dose-dependent decrease in cocaine infusions for both the 1- and 6-h access groups and having virtually no effect on food-maintained responding across the entire dose range. In contrast, a dose of 3.0 mg/kg LY379268 that decreased responding in the 1-h cocaine access group had no effect on responding maintained by food. The next higher dose of LY379268 (6.0 mg/kg), however, decreased food-maintained responding and responding of both the short-and long-access groups to an equivalent extent. With effective doses of each of the compounds, and particularly with BINA, the effects on the short-access cocaine group were greater—or the animals more sensitive—than those seen with the longer-access animals. The effects of BINA under the reinstatement procedure following extinction of food- or cocaine-maintained responding were consistent with the results just described: in those animals in which presentation of the stimulus previously associated with cocaine or food delivery engendered responding, BINA blocked the reinstatement of lever pressing in the animals that were previously maintained by cocaine, but did not affect the responding of those animals that previously responded under the food schedule. Thus, the selectivity of the effects of BINA on behavior maintained by cocaine and on stimulus- or cue-elicited responding holds up under two experimental conditions. Finally, in the experiments that addressed the effects on intracranial self-stimulation, it was found that BINA alone increased the threshold for electrical stimulation of the brain, whereas cocaine significantly lowered the threshold; BINA attenuated the effects of cocaine across the entire dose range.

Taken as a whole, this is an important step in the further identification and characterization of mGluR2 PAMS and for the setting of a potential therapeutic trajectory for the treatment of cocaine abuse. As such, it joins other potential compounds and targets such as the benztropine analogs that target the dopamine transporter (Tanda *et al*, 2009) and the σ-receptor (Hiranita *et al*, 2010). As seems to be the case with other disorders, individuals undergoing treatment for cocaine abuse are likely to be a heterogeneous population requiring a diverse armamentarium for effective treatment. The availability of compounds focusing on different targets and mechanisms provides a rich and valuable opportunity—as well as promise—for a long-awaited medication treatment approach to cocaine abuse. As is the case with many early-stage compounds, there are some questions that arise from the data to support moving BINA forward. Although the *in vitro* and *in vivo* profiles of BINA are impressive, some of the questions that remain to be addressed are the marked reduction in the half-life of the compound at the 40 mg/kg dose compared with the 20 mg/kg dose and the corresponding decreases in the volume of distribution and clearance at these doses. In light of the fact that the brain and plasma levels are also lower at the 40 mg/kg dose, it remains for further study to determine whether these findings might account for the differences observed in the short- and long-access rats and whether there may be active metabolites that are degrading BINA and limiting these levels at the higher doses. These are surmountable issues, if indeed they are issues at all, but the point made earlier remains: these are intriguing findings, integrating at one time a profile of activity that portends promising future developments for cocaine abuse treatment and perhaps other therapeutic avenues. Importantly, the approach speaks emphatically on the integrative power of collaborative academic science and drug discovery as a way of the future for an industry that has undergone tremendous transformation and has had varied success.

DISCLOSURE

The author currently serves on the Scientific Advisory Boards of Biogen-Idec and Dr Reddy's Laboratories; he has been a consultant to Cephalon, Sepracor, and Somnus.

REFERENCES

Galici R, Jones CK, Hemstapat K, Nong Y, Exhemendia NG, Williams LC *et al* (2006). 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* **318**: 173–185.

Hiranita T, Soto PL, Tanda G, Katz JL (2010). Reinforcing effects of σ-receptor agonists in rats trained to self-administer cocaine. *J Pharmacol Exp Ther* **332**: 515–524.

Jin X, Semenova S, Yang L, Ardecky R, Sheffler DJ, Dahl R *et al* (2010). The mGlur2 positive allosteric modulator BINA decreases cocaine self-administration and cue-induced cocaine-seeking and counteracts cocaine-induced enhancement of brain reward function in rats. *Neuropsychopharmacology* **35**: 2021–2036.

Johnson MP, Baez M, Jagdmann 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-ethoxyphenoxy)phenyl)-*N*-(2,2,2-trifluoroethylsulfonyl)pyrid-3-ylmethylamine. *J Med Chem* **46**: 3189–3192.

Marino MJ, Conn PJ (2006). Glutamate-based therapeutic approaches: allosteric modulators of metabotropic glutamate receptors. *Curr Opin Pharmacol* **6**: 98–102.

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.

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.

Tanda G, Newman AH, Katz JL (2009). Discovery of drugs to treat cocaine dependence: behavioral and neurochemical effects of atypical dopamine transport inhibitors. *Adv Pharmacol* **57**: 253–289.