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Metabotropic Glutamate Receptor 2 Positive Allosteric Modulators: Closing the Gate on Drug Abuse?

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Abnormally high levels of extracellular glutamate, the principal excitatory neurotransmitter in the central nervous system, have been implicated in elevated drug seeking and taking as well as drug addiction (1). Presynaptic metabotropic glutamate receptors (mGluRs) can limit glutamate release by acting as autoreceptors on glutamatergic terminals (2). Among the eight subtypes of mGluRs, group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR7, and mGluR8) are known to act as autoreceptors at excitatory synapses in the mammalian brain. Group II mGluRs have received considerable attention in recent years as contributing factors and therapeutic targets for drug abuse disorders (2). For example, several studies demonstrated that agonists of group II mGluRs decrease operant self-administration of drugs, including cocaine, alcohol, nicotine, and methamphetamine. In addition, activation of group II mGluRs attenuates cue-induced reinstatement of cocaine, heroin, alcohol, and methamphetamine self-administration as well as drug priming-induced reinstatement of nicotine, methamphetamine, and cocaine seeking. Conversely, an antagonist of group II mGluRs increases alcohol drinking (3). There is an evolving idea that presynaptic group II mGluRs may provide a “gatekeeper” function, limiting glutamate release at key synapses in addiction circuitry.

However, the crucial unanswered question concerning this hypothesis is the identity of the group II mGluR that modulates drug-related behaviors. The agonists and antagonists used in many studies do not discriminate between mGluR2 and mGluR3. Pharmacotherapeutic development requires determining which receptor or receptors play the primary role in this process. The development more recently of several mGluR2-selective positive allosteric modulators (PAMs) has enabled investigators to begin to delineate the specific role of mGluR2 in drug seeking and drug taking. Previously, the strong conservation of the glutamate binding site among mGluR subtypes presented a significant roadblock to developing subtype-selective agonists. Therefore, efforts to identify subtype-selective compounds shifted to discovery of allosteric modulators, which bind to distinct, less-conserved sites on the receptor and modulate the ability of glutamate to activate the receptor

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(4). In native tissues, PAMs typically do not directly activate the receptor, but instead enhance the ability of the endogenous ligand to activate the receptor (Figure 1). Using these novel tools, several investigators showed that selective enhancement of mGluR2 activity reduces cocaine self-administration and cue-induced reinstatement of cocaine seeking in rats, implicating mGluR2 as a key target for modulating drug abuse. Corroborating the idea that mGluR2 plays a role in drug-seeking and drug-taking behaviors, more recent studies demonstrated decreased mGluR2 function in response to chronic nicotine or alcohol exposure (5,6) as well as increased alcohol consumption in rats or mice lacking mGluR2 (3). It appears likely that the autoreceptor function of mGluR2 has a key role in controlling drug seeking and taking.

Two articles in the current issue of *Biological Psychiatry* reinforce and extend these findings in rodents and nonhuman primates. The major advance is that a highly selective, potent, and orally available mGluR2 PAM decreases measures of drug intake and relapse. The study by Justinova *et al.* (directed by the late Dr. Steven Goldberg) (7) focuses on pharmacologic characterization of the newly developed mGluR2 PAM AZD8529 (8) in cell lines and cynomolgus monkey (*Macaca fascicularis*) brains. The compound showed strong selectivity for mGluR2 relative to mGluR3 and a host of other neurotransmitter receptors. In addition, AZD8529 increased the ability of an mGluR2 and mGluR3 agonist to stimulate G protein activation in the monkey brain. The authors showed that intramuscular injection of AZD8529 decreased operant self-administration of nicotine in squirrel monkeys (*Saimiri sciurea*). This effect was dose-dependent, although it plateaued at a relatively low drug dose. The selectivity of AZD8529 for decreasing nicotine self-administration was encouraging, as doses that reduced nicotine self-administration did not produce alterations in food self-administration.

Presentation of cues associated with drug self-administration and delivery can become conditioned to support operant responses linked to drug self-administration. Following extinction of responding for drug, presentation of conditioned cues reinstates responding. Administration of AZD8529 reduced reinstatement of drug-seeking responses in squirrel monkeys previously trained and subsequently extinguished for nicotine-driven responding. Nicotine administration by the experimenter also reinstated responding, and this behavior was likewise decreased by AZD8529. Thus, enhancing the function of mGluR2 decreased the seeking and the taking of nicotine in nonhuman primates. Owing to the greater genetic and anatomic similarities between nonhuman primates and humans (as opposed to rodent models), studies performed in nonhuman primates could have improved predictive validity for preclinical evaluation. These findings in squirrel monkeys increase confidence that AZD8529 may have antiabuse potential in humans.

Caprioli *et al.* (9) examined the effects of AZD8529 on conditioned responding and incubation of cue-induced reinstatement of responding for methamphetamine in rat. The term incubation refers to a time-dependent increase in operant responding when conditioned cues are presented after training in cue-elicited operant behavior (in this case for drug reward) and subsequent forced abstinence. In this paradigm, cue-elicited drug seeking is more robust after several weeks of abstinence compared with shorter time points after abstinence. Caprioli *et al.* examined cue-induced reinstatement of responding in rats trained

to self-administer methamphetamine. Administration of AZD8529 reduced incubated responding 21 days into abstinence but did not alter the substantially weaker reinstatement of methamphetamine seeking after 1 day of abstinence. These authors also developed a voluntary abstinence paradigm in which rats were trained to self-administer palatable food before methamphetamine self-administration training. Subsequently, when given a choice between responding for food or methamphetamine, rats exhibited a strong preference for food and voluntarily abstained from methamphetamine self-administration. This procedure also resulted in incubated methamphetamine seeking, and reinstatement of drug seeking was decreased by AZD8529 after 21 days of voluntary abstinence. In contrast, nonincubated responding was not reduced. Similar to Justinova *et al.*, Caprioli *et al.* showed that AZD8529 does not alter operant responding for food. Collectively, these findings indicate that increasing mGluR2 activity can reduce reinstatement of drug-seeking behavior across multiple models of drug abuse as well as multiple species.

Use of the voluntary abstinence procedure is an intriguing aspect of the study by Caprioli *et al.* The findings with this paradigm indicate that enhanced cue control of drug responding occurs regardless of the trigger for abstinence. However, the fact that rats forego responding for methamphetamine when palatable food is available raises important questions about the relative desirability of the different rewards. Animal models of addiction have attempted to find conditions in which the drug exerts stronger behavioral control than other environmental factors. By this criterion, the rats examined in this study did not show evidence of robust drug preference or an “addiction-like” state. However, there is no objective index of addiction in rodent models, and thus it is important to characterize various behavioral phenotypes related to drug seeking and intake when assessing potential pharmacotherapies for drug abuse disorders. The lack of AZD8529 effect on day 1 of abstinence also raises questions about the ability of mGluR activation to reduce ongoing drug taking. However, the findings by Justinova *et al.* indicate that decreased drug-seeking and drug-taking behavior does not require incubation of craving, at least for nicotine in nonhuman primates. It is possible that mGluR2 PAMs may have differential effects on drug taking and relapse depending on the abused drug.

The use of an mGluR2 PAM rather than an agonist in these studies highlights several potential benefits of PAMs as therapeutic agents for treating drug abuse disorders. First, the efficacy of an mGluR2-selective drug clarifies the therapeutic potential of this specific receptor. In addition, the fact that PAMs enhance the effects of endogenous glutamate rather than persistently activate the receptor may prove advantageous because PAMs preserve the spatial and temporal actions of endogenous glutamate, which serves to fine-tune the receptor’s activity and potentially avoid receptor desensitization. Consequently, PAMs are predicted to be less susceptible than agonists to induction of tolerance after repeated dosing. A previous study demonstrating that the group II mGluR agonist LY379268 reduced nicotine self-administration in rats also showed remarkable tolerance to this effect, with nicotine self-administration levels returning to baseline within 2 weeks of daily LY379268 dosing (6). Justinova *et al.* did not see a reduction in the ability of AZD8529 to reduce nicotine self-administration after repeated dosing, lending support to the idea that PAMs may have an advantage over traditional agonists in terms of propensity to development of tolerance.

There is a growing idea in the field as a whole, as in the studies by Justinova *et al.* and Caprioli *et al.*, that excessive drug use may be controlled through activation or potentiation of mGluR2. However, this approach will ultimately have to be evaluated in humans. Toward this goal, at least two mGluR2 PAMs, AZD8529 and JNJ-40411813 (developed by Janssen Pharmaceuticals, Inc, Breese, Belgium, and Addex Therapeutics, Geneva, Switzerland) have been optimized for use in humans and evaluated in small-scale clinical studies. Both drugs were reported to be well tolerated (8,10). Results of clinical trials evaluating the ability of fully optimized mGluR2 PAMs to reduce drug taking and relapse after abstinence will be highly anticipated.

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Figure 1.

Enhanced metabotropic glutamate receptor 2 (mGluR2) activation by orthosteric agonists versus positive allosteric modulators (PAMs). **(A)** Traditional agonists of G protein-coupled receptors such as mGluR2 bind to the orthosteric binding site of the receptor. The receptor is persistently activated while bound to the drug and does not adhere to its normal temporal and spatial patterns of activation. **(B)** PAMs bind to sites on the receptor that are distinct from the binding site of the endogenous ligand and typically do not activate the receptor in the absence of the endogenous ligand. **(C)** In the presence of endogenous glutamate, the PAM enhances the effect of glutamate. This pharmacologic mechanism preserves the normal temporal and spatial pattern of receptor activation and may be less likely to cause receptor desensitization and drug tolerance.