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Accruing preclinical evidence about metabotropic glutamate 5 receptor antagonists as treatments for drug dependence highlights the irreplaceable contributions of animal studies to the discovery of new medications for human disorders

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Drug abuse and dependence on licit and illicit drugs continues to be a significant public health problem in the United States that leads to serious behavioral problems and health consequences (Substance Abuse and Mental Health Services Administration, 2008). In addition to psychosocial and cognitive behavioral therapies that are partially effective (e.g., Morgenstern and McKay, 2007), only few pharmacological treatments have demonstrated efficacy for treating drug addiction. Therefore, continuing intensive preclinical investigations have focused on the discovery of novel therapeutics for drug dependence. These investigations are fueled by accumulating knowledge about the neuronal processes that mediate the various effects of drugs of abuse and how chronic exposure to drugs of abuse alters brain function. Such advances in basic neuroscience knowledge lead to innovative hypotheses regarding the brain molecules and processes that need to be targeted to treat drug dependence and assist people in maintaining abstinence. In the context of summarizing the results of a research paper published in this issue of *Neuropsychopharmacology* (Gass *et al*., 2009), the purpose of the present commentary is to discuss how the data presented in this paper, generated using animal models of aspects of drug dependence, advance translational opportunities and potentially contribute to improved patient care (Markou *et al*.,2009).

Gass *et al*. (2009) showed that the metabotropic glutamate 5 (mGlu5) receptor antagonist 3-([2-methyl-1,3-thiazol-4-yl]ethynyl)pyridine (MTEP) decreased intravenous self-administration of the psychomotor stimulant methamphetamine in rats, reflecting diminished reward value of methamphetamine after MTEP treatment. Considering the close correspondence in the reward circuits that mediate drug reward in humans and rats (Kalivas and Volkow, 2005), one could predict that administration of MTEP, or another mGlu5

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Disclosures/Conflicts of Interest

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receptor antagonist, would also decrease methamphetamine consumption in humans. Furthermore, Gass *et al*. showed that MTEP decreased the motivation to work for methamphetamine infusions. Specifically, using the progressive-ratio schedule of reinforcement, in which the number of times that a rat needs to press a lever to receive a single drug infusion progressively increases, rats treated with MTEP stopped working for methamphetamine at a much lower number of responses than when treated with a vehicle solution. This result is potentially analogous to human drug addicts being willing to pay only a lower monetary price for a unit of drug when treated with a mGlu5 receptor antagonist than after placebo treatment, reflecting devaluation of the incentive value of methamphetamine after mGlu5 receptor antagonist treatment. Finally, the investigators used a procedure that is considered to be analogous to relapse to drug use in humans after a period of abstinence. In this procedure, rats that previously pressed a lever to self-administer methamphetamine infusions, that were always paired with the presentation of a brief stimulus light, stopped responding on the lever because methamphetamine was no longer available (i.e., extinction conditions). Subsequently, rats were presented with either the cue light previously associated with the delivery of a methamphetamine infusion or given an injection of methamphetamine. Both of these manipulations typically result in reinstatement of drug-seeking behavior expressed as increased responding on the lever, a behavior that previously led to methamphetamine self-administration. This test has been designed to be analogous to the human drug addict experience of exposure to environments and stimuli that previously predicted drug availability and use, or initial “tasting” of the previously abused drug. In humans, such experiences tend to lead to a sequence of drug-seeking behaviors (e.g., securing money, contacting a drug dealer, obtaining the drug and drug paraphernalia) that often lead to relapse to habitual drug use. Using the rat procedures described above, Gass and colleagues showed that treatment with MTEP prevented the reinstatement of drug-seeking behavior induced by either the presentation of the cues paired with methamphetamine or by methamphetamine administration itself. Finally, control experiments using identical procedures to those in the methamphetamine studies showed that MTEP had no effect on the rats’ behavior when food, rather than methamphetamine, was the reinforcer. The latter findings demonstrate that MTEP did not impair the ability of animals to locomote, perceive the stimuli, or perform the task. In summary, MTEP specifically decreased the reward value of methamphetamine, the motivation to self-administer methamphetamine, and “relapse” to drug-seeking upon re-exposure to methamphetamine or stimuli previously associated with methamphetamine administration, without impairing the ability of the animals to perform the various tasks or the value of a natural reinforcer.

As discussed above, the rat procedures used in this paper were selected by Gass and colleagues because they are highly analogous to experiences and situations encountered by human drug addicts. As such, these procedures have high translational value because they allow us to predict exactly for which aspects of methamphetamine dependence mGlu5 receptor antagonists may be efficacious in human methamphetamine addicts. Although an mGlu5 receptor antagonist that may gain approval as a medication for humans is likely to be a different compound than the ones used as tools in preclinical research, precise predictions can still be made based on the results of studies conducted in animal models of drug dependence. Based on the results of Gass and colleagues, human methamphetamine addicts treated with an mGlu5 receptor antagonist are predicted to be less motivated to consume methamphetamine and diminish its use, and they will be less likely to reinitiate drug use or seek drug upon encountering stimuli and situations that were previously associated with drug use. Even if relapse occurs, methamphetamine use is predicted to be less likely to escalate into a “binge,” which is the most common way of abusing psychostimulants.

However, additional preclinical work is required to address medication development issues that were not addressed by Gass and colleagues or previous work. An important question is whether tolerance may develop to these therapeutic effects of an mGlu5 receptor antagonist with chronic daily use because humans often need to take such medications chronically and daily. Tolerance develops to the reductions in intravenous nicotine self-administration induced by administration of an mGlu2/3 receptor agonist after six days of daily administration (Liechti and Markou, 2008). It is also not known how an mGlu5 receptor antagonist may affect symptoms of early methamphetamine withdrawal. Previous work has shown that the mGlu5 receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) had no effect on the anhedonia associated with early nicotine withdrawal (Liechti and Markou, 2008). The effects of mGlu5 receptor antagonism on the various aspects of methamphetamine withdrawal remain to be investigated. Because mGlu5 receptor antagonists have been shown to have anxiolytic properties (e.g., Tatarczynska *et al*., 2001), such compounds may possibly ameliorate anxiety symptoms associated with early psychostimulant withdrawal but not the depressive anhedonic symptoms.

As detailed above, accumulating evidence about the effects of mGlu5 receptor antagonists in drug dependence has high translational value and makes specific predictions about the putative efficacy of mGlu5 receptor antagonists for treating several aspects of psychostimulant dependence. Such preclinical work could potentially guide the design of early proof-of-concept studies in human psychostimulant addicts, including individuals dependent on tobacco smoking. Specifically, based on the preclinical findings reviewed above, an mGlu5 receptor antagonist is predicted to be efficacious in decreasing psychostimulant drug use and the probability of relapse but may not treat the anhedonic aspects of early psychostimulant withdrawal. Thus, the preclinical data could narrow the focus of studies in humans and consequently lead to demonstration of efficacy of mGlu5 receptor antagonists in treating specific aspects of psychostimulant dependence without unnecessarily spending resources studying aspects of dependence in which these compounds are unlikely to prove efficacious. The results of the human studies will inform preclinical animal model development such that the animal models improve their predictability of efficacy in humans and improve their utility and potential contribution to public health (Markou *et al*., 2009).

Interesting questions are why the authors specifically investigated the effects of an mGlu5 receptor antagonist and what prior evidence suggested that the mGlu5 receptor may be a good target for methamphetamine dependence. Extensive previous basic science investigations indicated an important role of glutamate transmission in psychostimulant dependence. A subsequent report showed that mutant mice lacking the mGlu5 receptor failed to acquire intravenous cocaine self-administration and exhibited no deficits in acquiring the same response to receive food (Chiamulera *et al*., 2001). This apparently serendipitous finding led to a series of investigations in laboratories throughout the world investigating the effects of mGlu5 receptor compounds on the effects of various drugs of abuse. The data presented in the paper by Gass and colleagues adds to the accruing literature about the efficacy of mGlu5 receptor antagonists in decreasing the rewarding and motivational properties of many drugs of abuse, as well as decreasing drug-seeking behavior. Specifically, it was previously shown that the mGlu5 receptor antagonist MPEP decreased nicotine and cocaine self-administration, and cocaine, morphine and amphetamine conditioned place preference in rats (for review, see Liecthi and Markou, 2008). Furthermore, MPEP decreased nicotine-seeking behavior, and the motivation to self-administer nicotine or cocaine in rats (for review, see Liechti and Markou, 2008). This historical perspective demonstrates how basic neuroscience knowledge about the function of glutamate in circuits mediating reward and motivational processes, together with an almost serendipitous finding in mutant mice that were originally created to study general brain

function of the mGlu5 receptor, led to extensive studies in a variety of animal models of dependence that clearly suggest the putative efficacy of mGlu5 receptor antagonists for the treatment of dependence on a variety of drugs of abuse. It is perhaps difficult to envision sometimes how a neuroanatomical finding about glutamatergic projections in limbic brain sites or electrophysiological findings about how a drug of abuse activates glutamate neurons or the creation and behavioral characterization of a mutant mouse (e.g., Chiamulera *et al*., 2001), or behavioral observations in healthy rats (e.g., Gass *et al*., 2008) inform patient care. Scientific progress occurs both with small incremental steps and huge leaps in knowledge and paradigm shifts (Kuhn, 1996) that together provide the building blocks for translational science designed to ensure that basic science findings will translate into benefits for patients (Markou *et al*., 2009).

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