

## REVIEW

# Negative Allosteric Modulators of Metabotropic Glutamate Receptors Subtype 5 in Addiction: a Therapeutic Window

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## Abstract

**Background:** Abundant evidence at the anatomical, electrophysiological, and molecular levels implicates metabotropic glutamate receptor subtype 5 (mGluR5) in addiction. Consistently, the effects of a wide range of doses of different mGluR5 negative allosteric modulators (NAMs) have been tested in various animal models of addiction. Here, these studies were subjected to a systematic review to find out if mGluR5 NAMs have a therapeutic potential that can be translated to the clinic.

**Methods:** Literature on consumption/self-administration and reinstatement of drug seeking as outcomes of interest published up to April 2015 was retrieved via PubMed. The review focused on the effects of systemic (i.p., i.v., s.c.) administration of the mGluR5 NAMs 3-((2-Methyl-4-thiazolyl)ethynyl)pyridine (MTEP) and 2-Methyl-6-(phenylethynyl)pyridine (MPEP) on paradigms with cocaine, ethanol, nicotine, and food in rats.

**Results:** MTEP and MPEP were found to reduce self-administration of cocaine, ethanol, and nicotine at doses  $\geq 1$  mg/kg and 2.5 mg/kg, respectively. Dose-response relationship resembled a sigmoidal curve, with low doses not reaching statistical significance and high doses reliably inhibiting self-administration of drugs of abuse. Importantly, self-administration of cocaine, ethanol, and nicotine, but not food, was reduced by MTEP and MPEP in the dose range of 1 to 2 mg/kg and 2.5 to 3.2 mg/kg, respectively. This dose range corresponds to approximately 50% to 80% mGluR5 occupancy. Interestingly, the limited data found in mice and monkeys showed a similar therapeutic window.

**Conclusion:** Altogether, this review suggests a therapeutic window for mGluR5 NAMs that can be translated to the treatment of substance-related and addictive disorders.

**Keywords:** glutamate, mGluR5, addiction, MPEP, MTEP

## Introduction

The significance of metabotropic glutamate receptor subtype 5 (mGluR5) for psychiatry is predetermined by its distribution and function. In the brain, mGluR5 density (Shigemoto et al., 1993) peaks in structures involved in motor coordination (Conn et al., 2005), reward-guided behavior (Russo and Nestler, 2013; Schultz,

2015), and substance-related and addictive disorders (Everitt and Robbins, 2005; Volkow et al., 2012). Furthermore, mGluR5 is critically implicated in normal and aberrant neuroplasticity (Kalivas, 2009; Luscher and Huber, 2010; Kalivas and Volkow, 2011) via structural and functional interactions with dopamine

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D1, D2, NMDA, adenosine A2, and GABA receptors (Conn et al., 2005; Bonsi et al., 2008). Its pharmacological properties have been thoroughly described (Conn and Pin, 1997; Ferraguti and Shigemoto, 2006), and selective pharmacological agents targeting the mGluR5 have been developed (Gasparini et al., 1999; Anderson et al., 2002). Preclinical research with these agents suggests that this receptor is a candidate target for the treatment of MDD (Markou, 2007; Pilc et al., 2008; Palucha-Poniewiera et al., 2013), Parkinson's disease (Marino et al., 2003; Johnson et al., 2009), schizophrenia (Conn et al., 2009; Herman et al., 2012), and addiction (Markou, 2007; Bird and Lawrence, 2009; Olive, 2009; Holmes et al., 2013; Pomierny-Chamiolo et al., 2014). The development of highly selective mGluR5 radiotracers such as [11C] ABP688 (Ametamey et al., 2006, 2007) has enabled the in vivo assessment of mGluR5 via positron emission tomography (PET) in humans (Terbeck et al., 2015). ABP PET-studies demonstrated altered mGluR5 binding in subjects with MDD (Deschwanden et al., 2011) and to a lesser extent in OCD (Akkus et al., 2014). However, the largest alteration in mGluR5 binding so far was found in smoking addiction (Akkus et al., 2013). It was replicated (Hulka et al., 2014) and extended by evidence for normalization of mGluR5 binding after prolonged smoking cessation (Akkus et al., 2015). Reduced mGluR5 binding was also found in cocaine addicts (Milella et al., 2014) and to a lesser extent in occasional cocaine users (Hulka et al., 2014), indicating a critical role for mGluR5 in human addiction and, consequently, in its treatment. Indeed, the introduction of selective and potent mGluR5 NAMs, such as 2-Methyl-6-(phenylethynyl)pyridine (MPEP) (Gasparini et al., 1999) and 3-((2-Methyl-4-thiazolyl)ethyl)pyridine (MTEP) (Anderson et al., 2002), has inspired a large and further growing number of experiments testing the effects of a wide dose range of different mGluR5 NAMs on various addiction models in mice, rats, and monkeys. From a clinical point of view, however, innovation stemming from preclinical research needs to be systematically examined for its translational potential (Markou et al., 2009). Here, we suggest 3 incremental requirements to be fulfilled to demonstrate a therapeutic potential for mGluR5 NAMs in substance-related and addictive disorders, based on animal model-studies: (1) addiction-like animal behavior should be reliably suppressed by mGluR5 NAMs; (2) moreover, there should be a clear-cut dose-response relationship allowing a prediction of which dose range and corresponding mGluR5 occupancy range is needed to reduce addiction-like behavior; and (3) finally, there should be a "therapeutic window" within which addiction-like animal behavior is suppressed without affecting responding to natural reinforcers. Previous reviews (Markou, 2007; Bird and Lawrence, 2009; Olive, 2009; Holmes et al., 2013; Pomierny-Chamiolo et al., 2014) have demonstrated the high efficacy of mGluR5 NAMs in reducing addiction-like behavior, as required by the first criterion. However, systematic reviews on the second and third requirements are still missing. To this end, we examined the literature on the effects of mGluR5 NAMs on self-administration of substances of abuse and food.

## Methods

Literature was collected using PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>) and the terms "mglur5" or "mglu5" followed by "self-administration" and either "cocaine," "nicotine," "ethanol," or "food." For food, this search scope was extended by entering only "mglur5" or "mglu5" and "food" to account for studies in which animals had free access to food, without the need to perform an operant response. Only publications in English within the scope of PubMed until April 2015 were

considered. Search results were narrowed down in 2 steps. First, only studies measuring consumption, self-administration, or reinstatement of food/drug seeking were included. In a second step, only reports on systemic, that is, i.p., s.c., or i.v. administration of mGluR5 NAMs were selected. Studies employing direct intracranial mGluR5 NAM administration to specific brain areas were excluded, since they cannot readily be translated to an established clinical administration routine and use an entirely different dose range.

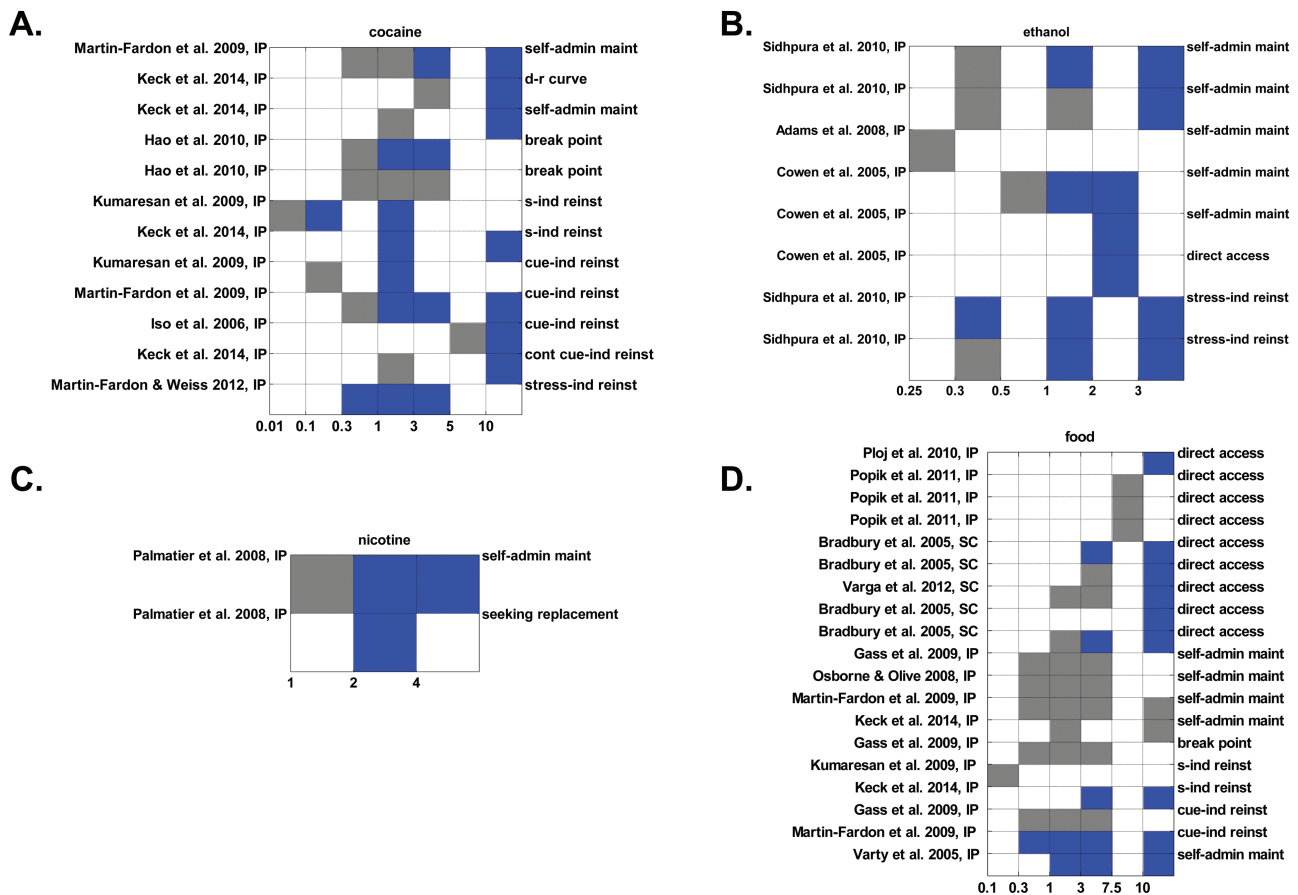
In studies with direct access, animals could consume food or ethanol without the need to perform operant responses to gain access to it, and consumption was measured as the outcome of interest after administration of mGluR5 NAMs or placebo. In self-administration studies, animals were trained to perform operant responses (eg, lever pressing or nose poking) to gain access to the reinforcer, which was delivered in a receptacle or intravenously, through an implanted catheter. In reinstatement studies, self-administration training was followed by extinction and, subsequently, reinstatement of drug seeking by either a priming administration of the reinforcer (substance-induced reinstatement) or a response-contingent administration of the conditioned cues that had been delivered together with the reinforcer during self-administration training (cue-induced reinstatement). Thus, the main experimental paradigms were consumption under direct access to the reinforcer, self-administration maintenance under a fixed reinforcement schedule, and substance- or cue-induced reinstatement of drug seeking.

A total of 125 reports (Chiamulera et al., 2001; Paterson et al., 2003; Backstrom et al., 2004; Tessari et al., 2004; Bespalov et al., 2005; Bradbury et al., 2005; Cowen et al., 2005; Kenny et al., 2005; Lee et al., 2005; McMillen et al., 2005; Olive et al., 2005; Paterson and Markou, 2005; Schroeder et al., 2005; Varty et al., 2005; Backstrom and Hyytia, 2006; Hodge et al., 2006; Iso et al., 2006; Lominac et al., 2006; Cowen et al., 2007; Liechti and Markou, 2007; Semenova and Markou, 2007; van der Kam et al., 2007; Adams et al., 2008; Besheer et al., 2008; Gupta et al., 2008; Osborne and Olive, 2008; Palmatier et al., 2008; Platt et al., 2008; Schroeder et al., 2008; Gass et al., 2009; Kumaresan et al., 2009; Martin-Fardon et al., 2009; Moussawi et al., 2009; Hao et al., 2010; Ploj et al., 2010; Sidhpura et al., 2010; Tronci et al., 2010; Eiler et al., 2011; Popik et al., 2011; Tronci and Balfour, 2011; Martin-Fardon and Weiss, 2012; Varga et al., 2012; Keck et al., 2013; Watterson et al., 2013; Keck et al., 2014) on the effects of mGluR5 NAMs were extracted and classified with respect to the following parameters: publication (source of the report), mGluR5 NAM (MPEP, MTEP, fenobam, or MFZ 10-7), species (rats, mice, or monkeys), administration route (i.p., s.c., i.m., or i.v.), administered dose (mg/kg), and experimental paradigm (supplementary Figures 1-4). Furthermore, the alpha error correction method reported was extracted for each study (supplementary Table 1). A focus on investigations administering MTEP or MPEP in rats was chosen, since the number of studies carried out in other species or with other mGluR5 NAMs was too low. To address criteria 1 and 2, as formulated above, 87 reports were extracted from 34 studies (supplementary Methods; supplementary Table 1). To address criterion 3, individual doses were aggregated in 3 dose ranges occupying <50%, 50% to 80%, or 80% to 100% of mGluR5. Dose ranges were chosen based on evidence that MTEP produces 50% to 80% mGluR5 occupancy when administered i.p. at 1.1 to 2 mg/kg and 100% occupancy at doses of 3 mg/kg or more, while MPEP produces 50% to 80% mGluR5 occupancy at 2.3 to 3.2 mg/kg i.p. and 100% occupancy at doses of 10 mg/kg or higher (Anderson et al., 2003; Urban et al., 2003; Busse et al., 2004; Steckler et al., 2005).

## Results

Robust evidence was found that both MTEP and MPEP suppress addiction-like behaviors for cocaine, ethanol, and nicotine (criterion 1) across various experimental models of addiction (Figures 1 and 2, A-C). In 47 of 52 reports (90%), a significant inhibiting effect of at least one of the administered mGluR5 NAM doses on addiction-like behavior in rats was found. This cannot be explained by “false positives” due to alpha error inflation caused by multiple comparisons for 2 reasons. First, statistical correction for multiple comparisons was applied in 30 of 34 studies (88%) (supplementary Table 1). Second, not a single report of statistically enhanced addiction-like behavior by treatment with any NAM dose was found. The graphical summary of these effects revealed a sigmoidal dose response-relationship (criterion 2): for each individual report there was a threshold below which the effect of no tested mGluR5 NAM dose reached statistical significance, whereas for all doses above this threshold, significant effects were observed. There was only one exception, where 1 and 10 but not 3 mg/kg MPEP i.p. inhibited cue-induced reinstatement of ethanol seeking in rats (Schroeder et al., 2008) (Figure 2B). Notably, the authors pointed out that

this finding was due to a single outlier in the 3-mg/kg treatment group (Schroeder et al., 2008). To explore this dose-response relationship with regard to receptor occupancy levels, all reports on cocaine, ethanol, and nicotine were pooled together in one larger group, substances of abuse, and individual doses were grouped in dose ranges according to mGluR5 occupancy levels (Figure 3). Only 21% of MTEP and 15% of MPEP doses producing <50% mGluR5 occupancy significantly inhibited addiction-like behavior (Figure 3A-B). In the dose range producing 50% to 80% mGluR5 occupancy, 71% of MTEP doses and 57% of MPEP doses significantly attenuated addiction-like behavior. This percentage grew further, reaching 84% for MTEP and 88% for MPEP in the dose range producing 80% to 100% mGluR5 occupancy. This dose-response relationship was similar yet not identical for different substances of abuse (supplementary Figures 5 and 6). MTEP in the dose range 1 to 2 mg/kg inhibited addiction-like behavior for cocaine and ethanol for 60% and 88% of doses, respectively (supplementary Figure 5). While 80% of MPEP doses in the range 2.5 to 3.2 mg/kg significantly inhibited addiction-like behavior for cocaine, 71% reduced addiction-like behavior in ethanol paradigms and 36% in nicotine paradigms (supplementary Figure 6).



**Figure 1.** The effects of 3-((2-Methyl-4-thiazolyl)ethynyl)pyridine (MTEP) on consumption, self-administration, and reinstatement of seeking of cocaine (A), ethanol (B), nicotine (C), and food (D). Left Y-axis labels indicate study citation and administration route. Right Y-axis labels indicate the experimental paradigm. X-Axis labels indicate the MTEP doses administered in mg/kg body weight. Blue squares indicate a significant reduction of the outcome measure and grey squares indicate non-significant effects, as reported by the authors. Empty (white) squares indicate that the respective dose has not been tested. Abbreviations: Abs-ind reinst, abstinence-induced reinstatement; Break point, analysis of break point under progressive reinforcement schedule; Cont cue-ind reinst, context- and cue-induced reinstatement; Cue- and s-ind reins, simultaneous cue- and substance priming-induced reinstatement; Cue-ind reinst, cue-induced reinstatement of food/drug seeking; D-r curve, dose-response curve; direct access, direct access to food/drug, with no operant responding needed; Schedule-ind reinst, schedule-induced reinstatement of food/drug seeking; seeking replacement, reinstatement by operant-response noncontingent experimenter-delivered reinforcers; self-admin maint, maintenance of food/drug self-administration; S-ind reinst, substance-induced reinstatement of food/drug seeking; Stress-ind reinst, stress-induced reinstatement of food/drug seeking.

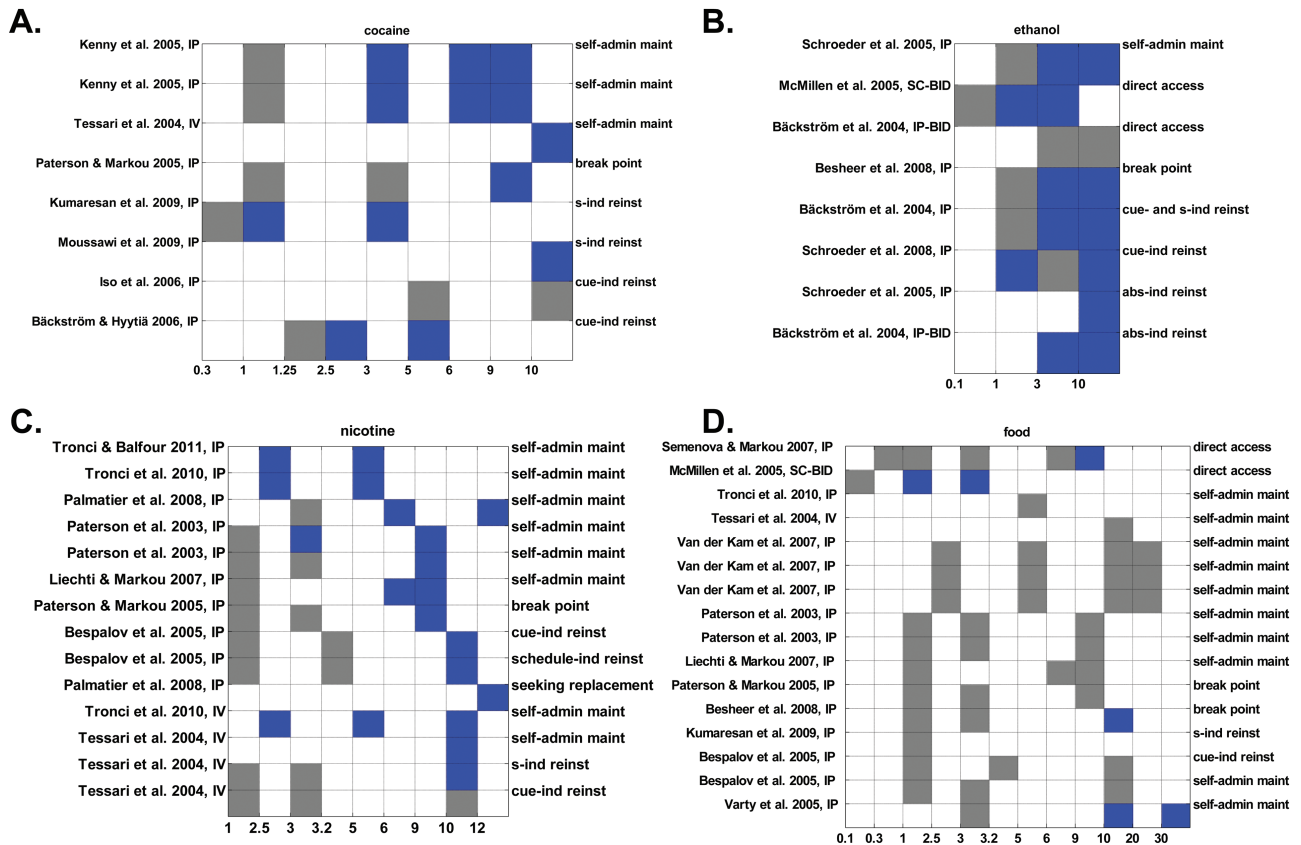


Figure 2. Effects of 2-Methyl-6-(phenylethynyl)pyridine (MPEP) on experimental paradigms employing cocaine (A), ethanol (B), nicotine (C), and food (D) as reinforcers. Color coding as in Figure 1.

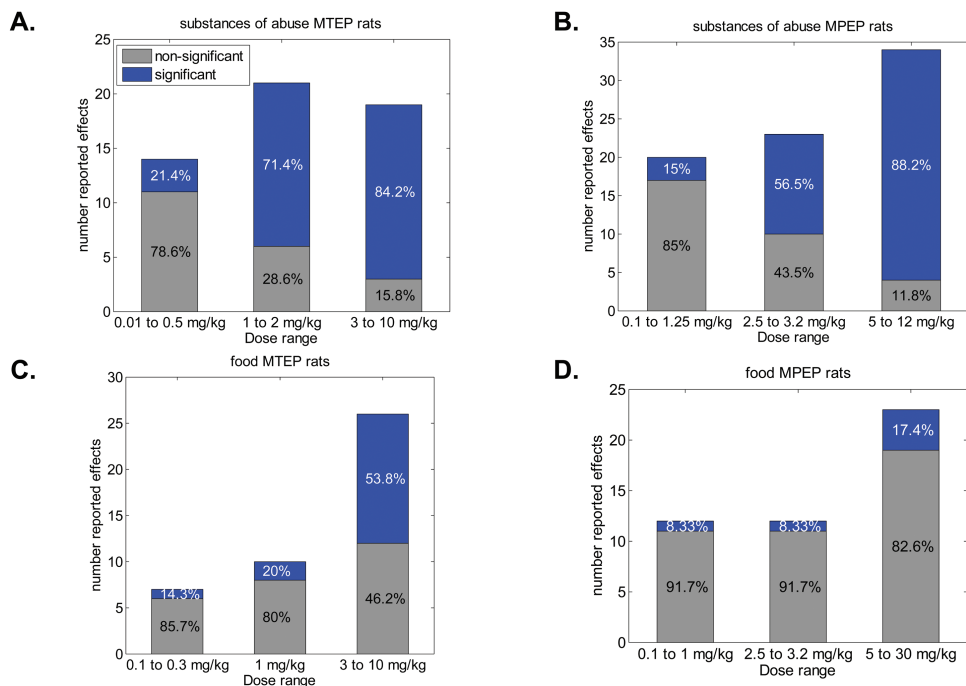


Figure 3. Dose dependency of the effects of 3-((2-Methyl-4-thiazolyl)ethynyl)pyridine (MTEP) in experimental paradigms employing cocaine, ethanol, or nicotine (A) as well as in food paradigms (C). Dose dependency of the effects of 2-Methyl-6-(phenylethynyl)pyridine (MPEP) in experimental paradigms employing cocaine, ethanol, and nicotine (B) as well as in food paradigms (D). Dose ranges have been chosen to reflect <50% mGluR5 occupancy (<1 mg/kg MTEP, <2.5 mg/kg MPEP), 50% to 80% mGluR5 occupancy (1–2 mg/kg MTEP, 2.5–3.2 mg/kg MPEP), and up to 100% mGluR5 occupancy (>2 mg/kg MTEP or >3.2 mg/kg MPEP).



Apparently, the effectiveness threshold for MPEP in nicotine paradigms is higher, around 5 mg/kg (Figure 2C).

Strikingly, both MTEP and MPEP showed much weaker effects in experimental paradigms employing food as a reinforcer (Figure 3C-D): significant effects for any of the mGluR5 NAM dose tested were found in 9 of 19 reports for MTEP (47%) and 3 of 16 reports for MPEP (19%) (Figures 1D and 2D). When taking the dose response-relationship into account, MTEP reliably inhibited food intake only at 10 mg/kg mGluR5. When considering only the dose range producing 50% to 80% receptor occupancy (1–2 mg/kg MTEP and 2.5–3.2 mg/kg MPEP), significant effects were found in 2 of 10 reports for MTEP and 1 of 12 reports for MPEP. In sum, MTEP and MPEP inhibit addiction-like behavior for cocaine, ethanol, and nicotine across different experimental paradigms without impairing food self-administration and consumption at doses producing 50% to 80% mGluR5 occupancy (criterion 3). Does this general finding hold when restricted to one outcome of interest? Analysis of reports on the effective doses of MTEP (1 mg/kg or more) and MPEP (2.5 mg/kg or more) showed that maintenance of self-administration was measured by far most frequently (supplementary Figures 7 and 8). Therefore, further analysis focused on this outcome of interest. The dose range 1 to 2 mg/kg MTEP significantly reduced self-administration maintenance in 5 of 9 cases (56%) for substances of abuse (0/2 cocaine, 4/5 ethanol, 1/2 nicotine) and 1 of the 5 cases (20%) for food (Figure 1). The dose range 2.5 to 3.2 mg/kg MPEP significantly reduced this outcome in 7 of 9 cases (78%) for substances of abuse (2/2 cocaine, 1/1 ethanol, 4/6 nicotine) and in none of 7 cases (0%) for food (Figure 2D). Taken together, 1 to 2 mg/kg MTEP and 2.5 to 3.2 mg/kg MPEP significantly inhibited self-administration maintenance for drugs of abuse in 12 of 18 cases (67%) and 1 of 12 (8%) cases for food self-administration (criterion 3). These effects are not altered by food restriction, which can increase glutamate receptor-mediated dopamine activity and is widely used in experimental protocols to enhance operant responding for drugs of abuse or food (Pothos et al., 1995;

Avena et al., 2008; Branch et al., 2013). mGluR5 NAMs inhibited maintenance of self-administration of cocaine, nicotine, or alcohol in 5 of 8 reports (63%) in which access to food was restricted (Paterson et al., 2003; Liechti and Markou, 2007; Palmatier et al., 2008; Tronci et al., 2010; Tronci and Balfour, 2011). Similarly, mGluR5 NAMs reduced self-administration maintenance for cocaine, nicotine, or alcohol in 7 of 10 reports (70%) in which animals had ad libitum access to food (Cowen et al., 2005; Kenny et al., 2005; Schroeder et al., 2005; Martin-Fardon et al., 2009; Sidhpura et al., 2010; Keck et al., 2014). Furthermore, mGluR5 NAMs did not impact self-administration of food, regardless of whether access to food was restricted or not (Figures 1D and 2D; supplementary Table 2). Based on these reports, we conclude that criterion 3 regarding the “therapeutic window” is met for maintenance of self-administration in rats.

Importantly, the limited evidence from studies in mice and monkeys supports the findings in rats (Figures 4 and 5). In mice, doses of 10 and 20 mg/kg MPEP reduced self-administration and consumption of ethanol without a reliable impact on self-administration and consumption of food (Figure 4B). Interestingly, this therapeutic range begins at 10 mg/kg, which produces 50% mGluR5 occupancy over 1 hour in mice and thus closely corresponds to the therapeutic dose range identified for MTEP and MPEP in rats (Anderson et al., 2003). Reports on the effects of MTEP on ethanol self-administration are less consistent but also limited in number, which warrants caution in their interpretation (Figure 4A). In monkeys, limited evidence suggests that 0.3 mg/kg MPEP i.m. suppress self-administration of cocaine but not food (Figure 5). Although these results have to be interpreted with caution due to the low number of reports available (supplementary Methods), they also suggest a therapeutic dose range for MPEP.

Finally, reports on the action of mGluR5 NAMs on methamphetamine and opiates is scarce and insufficient to draw firm conclusions. In rats, methamphetamine self-administration maintenance was reduced by i.p. 1 and 3 mg/kg, but not by

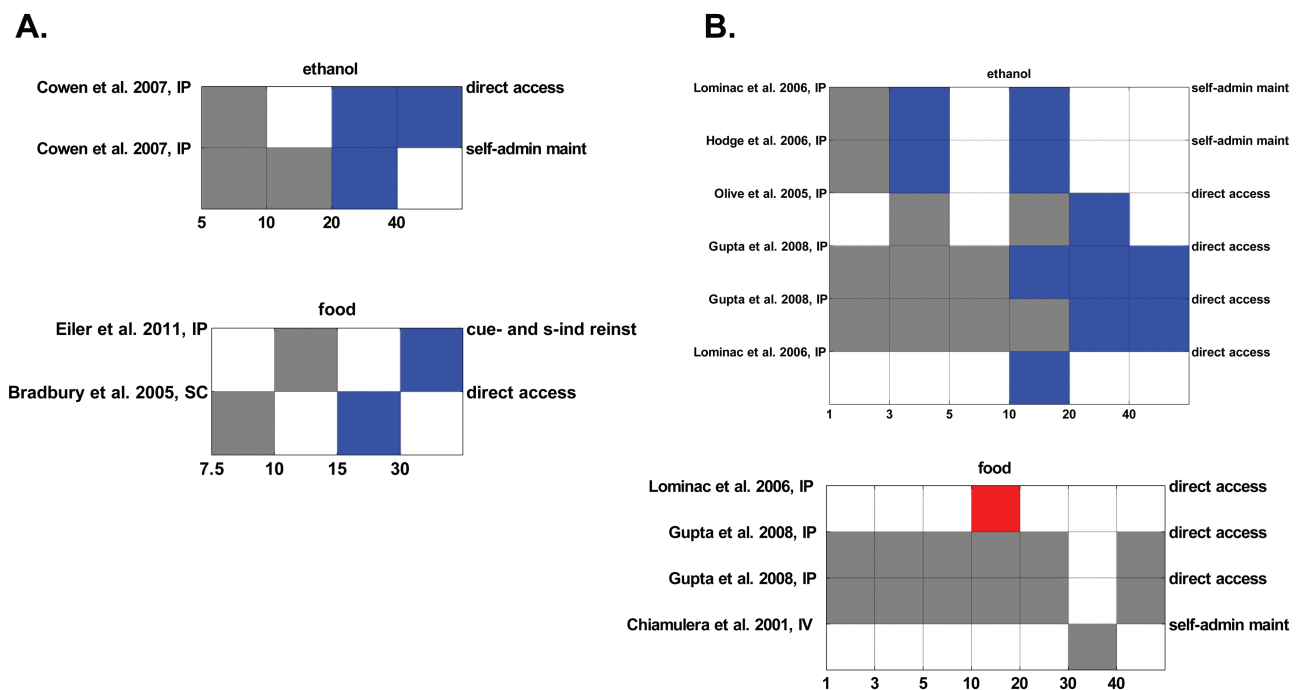


Figure 4. Effects of 3-((2-Methyl-4-thiazolyl)ethynyl)pyridine (MTEP) (A) and 2-Methyl-6-(phenylethynyl)pyridine (MPEP) (B) on self-administration and consumption of ethanol and food in mice. Color coding and axis labelling as in Figures 1 and 2. The red square indicates increased food intake after MPEP administration.

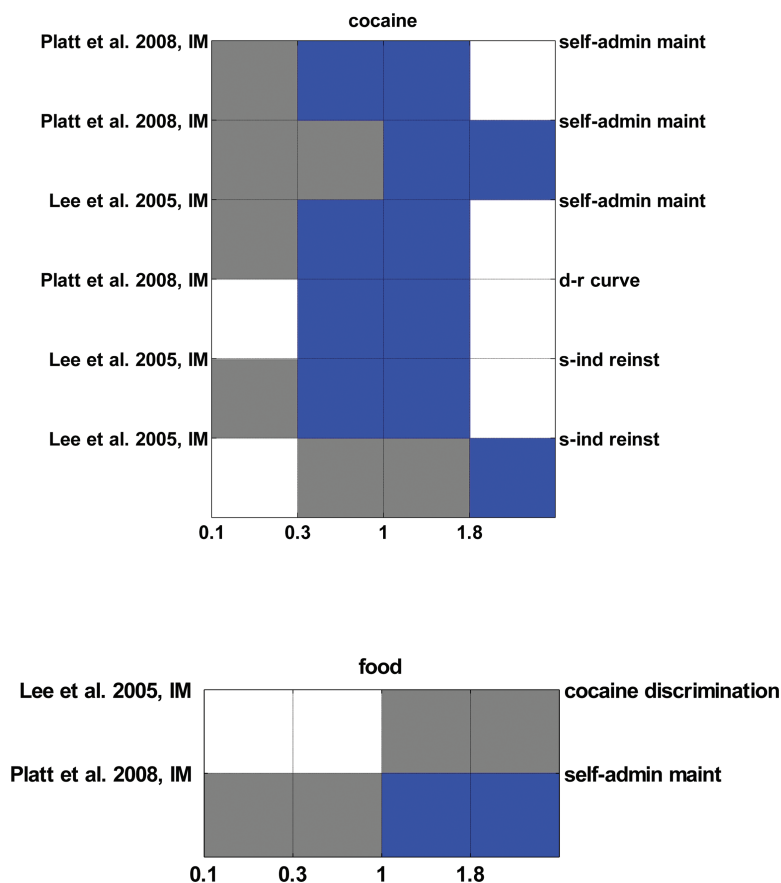


Figure 5. Effects of 2-Methyl-6-(phenylethynyl)pyridine (MPEP) on cocaine and food paradigms in monkeys. Color coding and axis labelling as in Figures 1 and 2.

0.3 mg/kg MTEP (Osborne and Olive, 2008). Another methamphetamine study in rats showed reduction of both substance-induced and cue-induced methamphetamine seeking by i.p. 1 and 3 mg/kg, but not by 0.3 mg/kg MTEP, while breaking point and self-administration maintenance were reduced by 3 mg/kg, but not by 0.3 and 1 mg/kg and MTEP (Gass et al., 2009). These results follow the same sigmoidal dose-response relationship and suggest that mGluR5 NAMs might reduce addiction-like behavior for methamphetamine in the therapeutic window outlined above. In mice, self-administration maintenance and cue-induced seeking for morphine were inhibited by a single i.p. dose of 20 mg/kg MTEP (Brown et al., 2012). In rats, heroin self-administration maintenance was inhibited by i.p. 20 but not 1.25, 2.5, 5, or 10 mg/kg MPEP (van der Kam et al., 2007). The last report suggests that generally higher mGluR5 doses might be needed to suppress heroin self-administration but should be interpreted with caution until corroborated and extended by further studies.

## Conclusions

This is the first systematic review to show that MTEP and MPEP reduce self-administration of cocaine, ethanol, and nicotine (criterion 1) at doses producing 50% to 80% mGluR5 occupancy (criterion 2) without impairing food self-administration (criterion 3). These results indicate a therapeutic potential for mGluR5 NAMs in the treatment of substance-related and addictive disorders.

Aggregating heterogeneous outcome measures, proverbially referred to as “comparing apples with oranges,” is a major methodological issue in systematic reviews (Leucht et al., 2009).

Indeed, different experimental paradigms, such as cue-induced reinstatement of drug seeking and maintenance of drug self-administration, can reflect different aspects of substance abuse disorders (Robinson, 2004; Koob et al., 2009) that warrant caution when making general statements about the effects of mGluR5 NAMs on addiction behavior. However, within the wide spectrum of the outcome measures reviewed here, evidence for the effects of mGluR5 NAMs on the maintenance of self-administration still holds when restricted to studies on self-administration of food or drugs of abuse. Self-administration paradigms are considered a model of binge-intoxication in human substance-related and addictive disorders (Koob et al., 2009) with high etiological and construct validity (Markou et al., 2009; O'Connor et al., 2011; Robbins, 2012). Furthermore, self-administration is a key behavioral element of substance abuse and addictive disorders (American Psychiatric et al., 2013). Therefore, the effects of mGluR5 NAMs on self-administration paradigms indicate a significant clinical impact if translated to the treatment of substance-related and addictive disorders.

The literature reviewed here clearly shows that MTEP reduces self-administration of cocaine, ethanol, and nicotine at lower doses (1–2 mg/kg) than MPEP (2.5–3.2 mg/kg). This finding is consistent with the higher mGluR5 occupancy rates produced by MTEP when administered at equal doses as MPEP (Anderson et al., 2003; Busse et al., 2004). A therapeutic window for MTEP and MPEP was identified at doses reported to produce approximately 50% to 80% mGluR5 occupancy (Anderson et al., 2003; Urban et al., 2003; Busse et al., 2004; Steckler et al., 2005), although a more recent investigation employing a different assessment method suggested lower and almost identical ED<sub>50</sub>

for these substances (Nagel et al., 2015). It is hard to identify the exact mGluR5 occupancy rate for an optimal ratio of reduction in substance of abuse self-administration to impairment in food consumption. However, the literature reviewed here suggests this occupancy rate is in the range 50% to 80%, as reported produced by i.p. administrations of 1 to 2 mg/kg MTEP or 2.5 to 3.2 mg/kg MPEP. Food consumption can be inhibited by MTEP but only when administered at doses more than 3 times higher than needed to block 100% mGluR5 for 1 hour (Anderson et al., 2003). Interestingly, MPEP can also inhibit food self-administration when administered at comparably high doses, that is, 10 to 30 mg/kg (Varty et al., 2005). It is important to point out that the dose ranges required for robust impact on food self-administration lie well outside of the therapeutic window and are likely irrelevant for the translation of mGluR5 NAMs to the treatment of substance-related and addictive disorders.

Self-administration of cocaine, ethanol, and nicotine, which greatly differ with respect to their pharmacodynamics, was reduced by similar levels of mGluR5 negative allosteric modulation. This finding indicates that mGluR5 NAMs act on a molecular final common pathway affected by these substances of abuse (Everitt and Robbins, 2005; Nestler, 2005; Koob and Volkow, 2010) rather than at their primary binding sites. According to the glutamate homeostasis hypothesis (Kalivas, 2009; Kalivas and Volkow, 2011), synaptic glutamate overflow activating mGluR5 drives together with reduced function of mGluR2/3 and glutamate/cysteine transporter pathological neuroplastic changes in the ventral striatum in addiction. The reduction in mGluR5 binding observed in human addiction (Akkus et al., 2013, 2015; Hulka et al., 2014; Martinez et al., 2014; Milella et al., 2014) can be thought of as a compensatory reaction (Kalivas, 2009).

This review focused on MTEP and MPEP because of the scarce literature on other mGluR5 NAMs. Both substances, however, have off-target effects that hinder their clinical application. MPEP is a competitive NMDA antagonist (O'Leary et al., 2000; Movsesyan et al., 2001), which may cause potentially severe side effects, such as hallucinations. Both MTEP and MPEP act as competitive inhibitors of the hepatic enzyme CYP1A2 and can cause clinically important interactions with substances metabolized by this enzyme, such as theophylline, caffeine, fluvoxamine, and olanzapine (Green et al., 2004). Both MTEP and MPEP are rapidly metabolized after administration (Keck et al., 2013). Other highly potent and selective mGluR5 NAMs, such as fenobam (Pecknold et al., 1982; Porter et al., 2005; Berry-Kravis et al., 2009), mavoglurant (Kumar et al., 2013; Stocchi et al., 2013; Reilmann et al., 2015), ADX10059, AZD2066 (Keywood et al., 2009; Zerbib et al., 2010, 2011; Rohof et al., 2012), and AZD9272 (Kalliomaki et al., 2013), have been investigated in humans for different indications and could find application in the treatment of addiction if their pharmacokinetics and side effect profiles prove favorable. Moreover, the industry continuously develops new compounds (Felts et al., 2009; Emmite, 2011; Kaae et al., 2012; Keck et al., 2012; Molck et al., 2012, 2014; Anighoro et al., 2015; Jaeschke et al., 2015; Lindemann et al., 2015) and new mGluR5-specific PET tracers (Yu, 2007; Mu et al., 2010; Sobrio, 2013), such as [18F]PSS232 (Sephton et al., 2015) and [18F]FPEB (Lim et al., 2014). These developments will inspire new preclinical and clinical research, which can build on the findings reported here by focusing on dose / receptor occupancy ranges that could more directly be translated to the clinic (Markou et al., 2009). On the one hand, different behavioral outcomes with incremental construct validity should be employed to investigate the action of mGluR5 on different aspects of human pathology (Koob et al., 2009). On the other hand, pharmacological small animal PET studies are

needed to show the longitudinal impact of substances of abuse and their pharmacological treatment on mGluR5.

Furthermore, clinical studies with mGluR5 NAMs conducted in accordance with the National Institute of Mental Health Research Domain Criteria (Insel et al., 2010, 2014) should consider cutting across disorders characterized by action-to-habit devolution (Fineberg et al., 2010; Robbins, 2012). These include substance abuse disorders (Everitt and Robbins, 2005) but also binge eating disorder (Smith and Robbins, 2013), bulimia nervosa (Calero-Elvira et al., 2009), and pathological gambling (Petry, 2006; Potenza, 2006; Leeman and Potenza, 2012). PET studies are needed to investigate the role for mGluR5 in these disorders (Akkus et al., 2013, 2014, 2015; Hulka et al., 2014; Milella et al., 2014), while clinical trials are needed to probe the therapeutic potential of mGluR5 agents. The results of this systematic review corroborate the feasibility of such pharmacological treatment by showing a therapeutic window for mGluR5 NAMs and suggest that research in this field should be further stimulated.

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## Statement of Interest

None.

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