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Metabotropic Glutamate Receptor 7 (mGluR7) as a Target for the Treatment of Psychostimulant Dependence

Xia Li and Athina Markou*

Department of Psychiatry, School of Medicine, University of California San Diego, La Jolla, CA, USA

Abstract

Although few medications have been approved by the U.S. Food and Drug Administration (FDA) to assist people to quit tobacco smoking, there are no FDA-approved medications to treat dependence on other psychostimulant drugs, such as cocaine. The motivation to maintain psychostimulant drug seeking and self-administration involves alterations in glutamatergic neurotransmission. Thus, medications that modulate glutamate transmission may be effective treatments for psychostimulant dependence. One presynaptic inhibitory glutamate receptor that critically regulates glutamate transmission is the metabotropic glutamate 7 receptor (mGluR7). This review summarizes nonhuman experimental animal data that indicate a critical role for mGluR7 in drug-taking and drug-seeking behaviors for the psychostimulants cocaine and nicotine. AMN082, the only commercially available allosteric receptor agonist, has been used to investigate the role of mGluR7 in psychostimulant dependence. Systemic administration or microinjection of AMN082 into brain sites within the mesocorticolimbic system decreased self-administration and reinstatement of both cocaine and nicotine seeking. *In vivo* microdialysis results indicated that a nucleus accumbens-ventral pallidum γ -aminobutyric acid-ergic mechanism may underlie AMN082-induced antagonism of the reinforcing effects of cocaine, whereas a glutamate mGluR2/3 receptor mechanism underlies the AMN082-induced blockade of cocaine seeking. These findings indicate an important role for mGluR7 in mesolimbic areas in modulating the reinforcing effects of psychostimulant drugs, such as nicotine and cocaine, and the conditioned behaviors associated with drugs of abuse. Thus, selective mGluR7 agonists or positive allosteric modulators may have the potential to treat psychostimulant dependence.

Keywords

Addiction; AMN082; cocaine; drug discovery; glutamate; mGluR7; nicotine

INTRODUCTION

Drug addiction is a chronic cognitive disorder that is characterized by compulsive drug use and drug seeking [1, 2]. Glutamatergic neurotransmission in the mesocorticolimbic pathway

*Address correspondence to this author at the Department of Psychiatry, M/C 0603, School of Medicine, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0603, USA; Tel: 858 534 1572; Fax: 858 534 9917; amarkou@ucsd.edu.

CONFLICT OF INTEREST

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has been hypothesized to be critically involved in the various effects of psychostimulant drugs, including the rewarding effects, development of dependence, and motivation to initiate and maintain drug-seeking behavior after protracted abstinence [3–5]. These actions of psychostimulant drugs support the acquisition and maintenance of the addictive behaviors, in which: (i) the rewarding effects drive the acquisition of drug taking and initial maintenance of drug use through positive reinforcement processes; (ii) the development of drug dependence drives chronic continued drug use and prevents quitting through negative reinforcement mechanisms; and (iii) the reinstatement of drug seeking, induced by the presentation of stimuli previously associated with the drug administration or the readministration of the drug itself, drive relapse to drug taking [6]. A large body of evidence has indicated that the inhibition of glutamatergic transmission through various means attenuates psychostimulant-induced behavioral effects in animal models with relevance to drug dependence [3–5, 7]. These findings confirm an important role for increased glutamate transmission in these crucial aspects of psychostimulant dependence and suggest that the pharmacological manipulation of glutamate transmission may be effective in blocking the reinforcing effects of drugs of abuse and preventing the reinstatement of drug seeking [3, 5, 8].

Metabotropic glutamate receptors (mGluRs) are of particular interest as potential therapeutic targets for psychostimulant dependence. Ionotropic glutamate receptors are ubiquitously involved in fast excitatory synaptic transmission throughout the brain, and the blockade of ionotropic glutamate receptors may be associated with severe adverse effects, including neurotoxicity and psychotogenicity [9]. However, mGluRs are slow-acting and modulate glutamate transmission by regulating neuronal excitability, synaptic transmission, and plasticity [10]. Therefore, targeting mGluRs may be more likely to induce the desired therapeutic effects with minimal side effects than targeting ionotropic glutamate receptors [4, 7, 11, 12]. Using selective pharmacological tools, we and others have demonstrated that decreasing glutamatergic neurotransmission by blocking postsynaptic Group I mGluR5 or activating presynaptic inhibitory Group II mGluR2/3 decreased the rewarding and motivational effects of drugs of abuse, such as cocaine, nicotine, morphine, heroin, and alcohol, with a potentially acceptable side effect profile [4, 7, 12–15]. This review article summarizes the role of presynaptic Group III mGluR7 in drug-taking and drug-seeking behaviors that involve the psychostimulants cocaine and nicotine.

mGluR7 IN THE BRAIN

Similar to all mGluRs, mGluR7 is a member of G-protein-coupled receptor family C, which consists of an extracellular N-terminal domain, heptahelical transmembrane domain, and intracellular C-terminals [16]. The competitive ligands, including orthosteric agonists and antagonists, bind to the extracellular domain. Noncompetitive ligands, including allosteric positive and negative modulators, bind to the transmembrane domain. Developing highly selective agonists or antagonists for specific mGluR subtypes is challenging because of the high conservation of glutamate binding sites across members of this receptor family and restricted structural requirements for pharmacophores that occupy this binding pocket [17]. By contrast, allosteric binding sites might exhibit greater structural divergence across this receptor family and provide opportunities to develop highly selective modulators [10].

mGluR7 couples $G_{i/o}$ proteins and inhibits Ca^{2+} channels and adenylate cyclase activity, thereby decreasing neurotransmitter release [16].

mGluR7 belongs to Group III mGluRs, that also includes mGluR4, mGluR6, and mGluR8. Among the Group III mGluRs, mGluR7 has the highest density in brain regions involved in reward, cognition and emotion, such as the dorsal striatum, nucleus accumbens (NAc), hippocampus, amygdala, ventral pallidum (VP), amygdala, olfactory bulb, locus coeruleus, and ventral tegmental area (VTA) [16]. This anatomical distribution of mGluR7 suggests that these receptors play a critical role in modulating neurotransmitter release in pathways that are involved in drug dependence. mGluR7 is primarily localized presynaptically and acts as an autoreceptor that regulates glutamate release and as a heteroreceptor that regulates the release of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) and possibly the release of monoamines also [18, 19]. Postsynaptic mGluR7 may be involved in regulating *N*-methyl-D-aspartate (NMDA) receptor trafficking and function [20]. mGluR7 plays a critical role in shaping synaptic responses for glutamatergic neurotransmission because these receptors are located directly in the presynaptic zone of the synaptic cleft of glutamatergic synapses [18, 19]. Unlike mGluR4 and mGluR8, mGluR7 has low affinity for glutamate and can only be activated when extracellular glutamate concentrations are sufficiently high [21]. This property of mGluR7 suggests that this receptor is a key player in the regulation of glutamate release during intense synaptic activity. Supporting this notion, mGluR7 knockout mice exhibited an increased susceptibility to convulsive seizures [22], and the disruption of mGluR7 signal transduction induced absence epilepsy-like seizures in rats and mice [23]. Given that increased glutamate transmission mediates the reinforcing and motivational effects of psychostimulants and reinstatement of drug seeking, the modulatory role of mGluR7 that depends on hyperglutamatergic activity suggests the potential utility of this receptor subtype in blocking the reinforcing and motivational effects of psychostimulant drugs that increase glutamate release. Moreover, mGluR7 is the most highly conserved receptor subtype among all mGluRs across mammalian species [16], suggesting that results with mGluR7 pharmacological agents in experimental animals are likely to generalize to humans.

mGluR7 LIGANDS

The first selective mGluR7 allosteric agonist, AMN082 (*N,N'*-dibenzhydrylethane-1,2-diamine dihydrochloride), was identified in 2005 using a random high-throughput screen of chemical libraries [24]. AMN082 has ~30–150 folds selectivity for mGluR7 over other mGluRs, NMDA receptors, and α -amino-3-hydroxy-5-methyl-4-isoxale propionate (AMPA) receptors [24]. It is also highly potent in inhibiting the accumulation of cyclic adenosine monophosphate (cAMP) in mGluR7-expressing cells, with an EC_{50} value of ~64–290 nM, and enhancing guanosine 5'-*O*-[γ -thio]triphosphate ($GTP\gamma S$) binding by over 160% relative to the maximal activity of L-glutamate [24]. Most importantly, AMN082 is orally active and readily penetrates the blood-brain barrier [24]. Thus, AMN082 has been a valuable pharmacological tool for assessing the function of mGluR7 [17]. The first selective mGluR7 allosteric antagonist, MMPIP (6-[4-methoxyphenyl]-5-methyl-3-pyridin-4-ylisoxazolo[4,5-*c*]pyridin-4[5*H*]-one), was identified in 2007 [25]. MMPIP blocked intracellular Ca^{2+} mobilization ($IC_{50} = 20$ nM) and forskolin-stimulated cAMP

accumulation ($IC_{50} = 99$ nM) induced by L-(+)-2-amino-4-phosphonobutyric acid (L-AP4; a Group III mGluR agonist) in cells that express rat mGluR7 [25]. MMPIP also antagonized the AMN082-induced inhibition of cAMP accumulation, suggesting that MMPIP shares the same binding site with AMN082 in the transmembrane domain [25]. Most recently, another mGluR7 negative allosteric modulator, ADX71743 ([+]-6-[2,4-dimethylphenyl]-2-ethyl-6,7-dihydrobenzo[d]oxazol-4[5H]-one), was identified by Addex Therapeutics [26]. ADX71743 attenuated L-AP4-induced Ca^{2+} mobilization in cells that express rat ($IC_{50} = 63$ nM) and human ($IC_{50} = 88$ nM) mGluR7 [26]. The first mGluR7 orthosteric antagonist, XAP044 (7-hydroxy-3-[4-iodophenoxy]-4H-chromen-4-one), was identified by Novartis [27]. XAP044 reduced L-AP4-induced GTP γ S binding ($IC_{50} = 2.8$ – 3.5 μ M) but had no effect on AMN082-induced GTP γ S binding in mGluR7-expressing cells [27]. Among these four mGluR7 ligands, only AMN082 and MMPIP are commercially available. Thus, we investigated the involvement of mGluR7 in psychostimulant dependence using these two compounds. Notably, after we published papers that reported the effects of AMN082 on cocaine dependence, subsequent studies indicated that some of the effects of AMN082 may not be attributable to mGluR7 but rather to monoamine reuptake inhibition by an AMN082 metabolite [28, 29]. However, in our cocaine studies, AMN082 was centrally injected into specific brain sites, thus avoiding the nonspecific effects induced by the metabolite. Moreover, the selective antagonist MMPIP was applied in these central injection studies to confirm the specificity of the effects of AMN082-induced mGluR7 activation on cocaine dependence. AMN082 was also shown to induce robust mGluR7 internalization in dissociated hippocampal cultured neurons [30], which may translate into functional antagonism of the receptor when this compound is administered chronically.

mGluR7 AND PSYCHOSTIMULANT REINFORCEMENT

The positive reinforcing effects of psychostimulants drive the acquisition and maintenance of drug use [31, 32]. The fact that addictive drugs serve as reinforcers in maintaining operant drug-taking behavior led to the development of the intravenous drug self-administration procedure, which provides a reliable animal model that has good construct validity for drug-taking behaviors in humans [33, 34]. The fixed ratio (FR) schedule of reinforcement assesses the primary reinforcing effects of drugs of abuse. The progressive ratio (PR) schedule of reinforcement assesses both drug-taking and incentive motivation for drugs of abuse [33, 34]. A common property of all drugs of abuse from various pharmacological classes is the enhancement of brain reward function, assessed in the intracranial self-stimulation (ICSS) procedure [35]. This action may partly account for the intrinsic rewarding properties of drugs of abuse and reflect how drugs increase the sensitivity to nondrug rewarding environmental stimuli [35].

The systemic administration of AMN082 (3, 10, and 20 mg/kg) decreased cocaine self-administration under both FR and PR schedules of reinforcement in rats [36], suggesting that AMN082 not only inhibits the primary reinforcing effects of cocaine and thus cocaine consumption but also inhibits the motivational effects of cocaine. Similarly, AMN082 inhibited ethanol self-administration in mice [37] and ethanol consumption and preference in rats [38]. Furthermore, mGluR7 knockout mice exhibited an increase in ethanol consumption [39]. However, this compound had no effect on sucrose-maintained responding

[36] or saccharin fluid intake [38], suggesting that AMN082 specifically inhibits the rewarding effects of drugs of abuse but not those of nature reinforcers, and this inhibition was not attributable to nonspecific locomotor effects or cognitive impairment. Consistent with this conclusion, AMN082 had no effect on ICSS thresholds by itself but attenuated the ICSS threshold-lowering effects of acute cocaine in rats [36]. This finding suggests that AMN082 produces neither reward-like nor aversive-like effects on brain reward function but blocks the reward-enhancing effects of cocaine. Furthermore, AMN082 inhibited cocaine-induced increases in locomotor activity in mice [40] but not rats [36]. However, it should be noted that 3 hr of locomotion were assessed after cocaine administration in the rat study, whereas 30 min locomotion was analyzed in the mouse study. If the 30 min locomotion data were used for analysis in the rat study, most likely an inhibitory effect of AMN082 on cocaine-induced hyperlocomotion would be found, based on the time-course data shown in the same paper.

Although, some studies have shown that AMN082 did not affect basal locomotor activity [36, 38, 40], other reports have shown that AMN082 (10 mg/kg) produced a transient (5–10 min) decrease in basal locomotor activity in rats [28] and mice [37, 41]. Moreover, chronic administration of AMN082 had no effect on locomotion [40]. Furthermore, high doses of AMN082 may impair locomotor coordination because 20 mg/kg AMN082 inhibited fast-running rotarod performance [36]. However, the inhibitory effects of AMN082 on cocaine taking are likely not attributable to impairments in locomotion or coordination because: (i) the AMN082-induced decrease in locomotion is very short (5–10 min) compared to the duration of the cocaine self-administration session (3 hr); and (ii) drug self-administration is a low-rate operant behavior that does not require precise locomotor coordination.

Furthermore, central injections of AMN082 into the NAc and VP, but not the dorsal striatum, decreased cocaine self-administration. Intra-NAc administration of the mGluR7 negative modulator MMPIP prevented the AMN082-induced decrease in cocaine self-administration [36]. Taken together, these results suggest that the inhibitory effects of AMN082 on cocaine reinforcement are at least partially mediated by the activation of mGluR7 in the NAc-VP pathway. To identify neuromechanisms that underlie the actions of AMN082, *in vivo* microdialysis studies were conducted with probes located in the NAc and VP. Systemic, intra-NAc, and intra-VP injections of AMN082 did not alter basal or cocaine-induced increases in extracellular dopamine in either naive or cocaine-experienced rats, suggesting a non-dopaminergic mechanism of action of AMN082 [36]. One hypothesis is that inhibition of medium-spiny GABAergic output neurons in the NAc, that predominantly project to the VP [42, 43], serve as one of the final common pathways that mediate psychostimulant reward [31, 44, 45]. Increased NAc dopamine levels induced by cocaine produces inhibitory effects on these medium-spiny GABAergic output neurons, mainly acting through postsynaptic inhibitory dopamine D₂ receptors, thereby decreasing extracellular GABA levels in the VP ([36, 42, 45–47] (for a detailed description and schematic diagram of the NAc-VP pathway, see [45])). Strikingly, AMN082 pretreatment attenuated cocaine-induced decreases in VP GABA release in both naive and cocaine-experienced rats [36], suggesting that a NAc-VP GABAergic mechanism may underlie AMN082-induced antagonism of the rewarding and motivational effects of cocaine.

Additional studies indicated that AMN082 enhanced the excitability of NAc GABAergic neurons by decreasing extracellular GABA and increasing extracellular glutamate levels in the NAc, thereby antagonizing the cocaine-induced inhibition of medium-spiny GABAergic neurons [36, 45].

In addition, systemic or intra-VTA administration of AMN082 significantly decreased nicotine self-administration in rats (A. Stoker, A. Markou, and X. Li, unpublished data). Most interestingly, the inhibitory effects of AMN082 on nicotine reinforcement were more potent than those on cocaine reinforcement. A plausible explanation for the increased sensitivity of nicotine self-administration, relative to cocaine self-administration, to the effects of AMN082 is the fact that both mGluR7 and nicotinic acetylcholine receptors (nAChRs) are located on glutamatergic neurons in the VTA; thus, the interaction between mGluR7 agonism and nAChR activation on the same glutamatergic terminal may be more direct and effective than interactions between mGluR7 and the primary sites of action of cocaine, which are mainly monoamine transporters.

Altogether, findings indicated that the activation of presynaptic mGluR7 by AMN082 inhibited the reinforcing and motivational effects of cocaine and nicotine and attenuated the reward-enhancing effects of cocaine. These data are consistent with previous findings showing that decreasing glutamate transmission by activating presynaptic mGluR2/3 or blocking postsynaptic mGluR5 inhibited the reinforcing effects of cocaine [48–53] and nicotine [49, 50, 54, 55].

mGluR7 AND THE REINSTATEMENT OF COCAINE AND NICOTINE SEEKING

The high rate of relapse to drug-taking and drug-seeking behavior even after prolonged periods of abstinence is a major hurdle in the treatment of drug addiction. In both humans and experimental animals, re-exposure to drugs of abuse, the presentation of environmental stimuli (cues) that are previously associated with drug taking, and environmental stressors can augment the vulnerability to relapse [56–58]. The extinction-reinstatement procedure in experimental animals is a putative model of relapse in humans [59], and has been extensively used to evaluate potential targets for preventing relapse. Thus, we used this procedure to assess whether the activation of mGluR7 by AMN082 has similar efficacy against drug-seeking behaviors as it does against drug-taking behaviors.

Systemic or intra-NAc administration of AMN082 significantly blocked the cocaine (10 mg/kg) priming-induced reinstatement of cocaine-seeking behavior in rats [60]; moreover, the mGluR7 negative modulator MMPIP blocked this effect. These findings suggest that the blockade of cocaine seeking by AMN082 is mediated by the activation of mGluR7 in the NAc. However, 20 mg/kg AMN082 also attenuated the sucrose-induced reinstatement of sucrose seeking, indicating that the highest dose of AMN082 nonspecifically inhibited the reinstatement of seeking behavior for both cocaine and natural reinforcers. This finding is consistent with those seen after administration of the mGluR2/3 agonist LY379268 that showed that LY379268 attenuated both nicotine- and food-seeking behavior [55]. Taken together, these observations suggest that glutamate-dependent mechanisms are involved in

conditioned behavioral responses, regardless of the reinforcer. However, unlike LY379268, which exhibited similar efficacy in attenuating nicotine- and food-conditioned responses, AMN082 more potently blocked the conditioned motivation for drug than for sucrose. A lower dose of AMN082 (10 mg/kg) selectively inhibited cocaine seeking but not sucrose seeking. Moreover, repeated psychostimulant exposure produced enduring neuroadaptations in glutamate transmission that are thought to contribute to relapse [3]. For example, cocaine and nicotine self-administration downregulated mGluR2/3 expression and/or function in the mesocorticolimbic system [55, 61]. Thus, mGluR7 expression or function is also likely altered in the psychostimulant dependent state, and the effects of an mGluR7 agonist are superimposed on this altered glutamatergic state that is not seen in sucrose-seeking rats. Therefore, mGluR7 ligands may be far more potent in modulating drug-related responses while minimally affecting the motivation and seeking for natural reinforcers.

Increases in glutamate transmission have been shown to underlie the reinstatement of drug-seeking behavior [3, 8]. We and others have demonstrated that cocaine priming or cocaine-associated cues significantly increased extracellular glutamate in the NAc [60, 62]. Interestingly, *in vivo* microdialysis assessment during the behavioral testing of reinstatement indicated that AMN082 attenuated both cocaine priming-induced increases in extracellular glutamate in the NAc and the reinstatement of cocaine-seeking [60]. This antagonism of cocaine seeking and cocaine-induced increase in glutamate release was blocked by systemic or intra-NAc administration of the mGluR2/3 antagonist LY341495. Altogether, these results suggest that a glutamate-mGlu2/3 receptor mechanism underlies the antagonism of cocaine seeking by AMN082.

In addition, systemic, intra-NAc or intra-VTA administration of AMN082 significantly inhibited cue-induced reinstatement of nicotine-seeking behavior in rats (A. Stoker, A. Markou, and X. Li, unpublished data), suggesting an important role for mesocorticolimbic mGluR7 in the development of nicotine dependence. Altogether, findings indicate that activation of presynaptic mGluR7 by AMN082 inhibits the reinstatement of cocaine- and nicotine-seeking behavior. These results are consistent with previous findings showing that decreasing glutamate transmission by activating presynaptic mGluR2/3 or blocking postsynaptic mGluR5 inhibited the reinstatement of cocaine seeking [63, 64] and nicotine seeking [55, 65].

mGluR7 AND OTHER PSYCHIATRIC DISORDERS

In addition to drug addiction, Group III mGluRs have been demonstrated to have anticonvulsive, anxiolytic, and analgesic properties and the potential to prevent excitatory injury [66]. As the most widely distributed Group III subtype, mGluR7 appears to be engaged in these actions. Accumulating evidence indicates that mGluR7 may be a promising target for the development of novel therapeutics to treat depression and anxiety [29, 41, 67–69].

AMN082 increased plasma corticosterone and corticotrophin levels in wildtype mice but not mGluR7-deficient mice [24], suggesting that mGluR7 plays an important role in stress-related psychiatric disorders, such as depression and anxiety. However, findings on the role

of mGluR7 in depression and anxiety have been contradictory. AMN082 produced anxiolytic-like effects in the modified stress-induced hyperthermia and four-plate test in wildtype, but not mGluR7 knockout, mice [70], impaired conditioned fear learning and enhanced its extinction [71–73], and facilitated between-session fear extinction [74]. AMN082 was also shown to have antidepressant-like effects in the forced swim and tail suspension tests in both mice and rats [29, 41, 67–69]. However, these pharmacological findings with AMN082 contradict those that used genetic manipulations and novel recently synthesized mGluR7 antagonists. Specifically, mGluR7 knockout mice exhibited an antidepressant-like phenotype and deficits in fear extinction [75–77]. The downregulation of mGluR7 in the adult mouse brain by short interfering RNA attenuated the extinction of learned aversion [71] and decreased anxiety-like behavior in the light-dark box, stress-induced hyperthermia, and fear-potentiated startle [78]. Moreover, XAP044, a new selective mGluR7 antagonist, reduced freezing during the acquisition of conditioned fear and showed anxiolytic-like efficacy in the stress-induced hyperthermia test and elevated plus maze in rodents [27]. Furthermore, a new mGluR7 negative allosteric modulator, ADX71743, induced anxiolytic-like effects in the elevated plus maze and marble burying test but had no effect in the forced swim test in mice [26].

Several factors may contribute to these conflicting results, including the off-target effects produced by an AMN082 metabolite [28, 29], the potential receptor internalization induced by AMN082 [30], and genetic compensation and adaptations during the early development of gene knockout mice. Overall, these intriguing findings strongly suggest the critical role of glutamate transmission and potential involvement of mGluR7 in depression and anxiety. Given that anxiety and depression are major negative affective signs of psychostimulant withdrawal that are hypothesized to greatly contribute to the persistence of drug taking and relapse to drug seeking [79], mGluR7 may also be a valuable target to alleviate these withdrawal symptoms, and thus promote abstinence.

CONCLUSION AND IMPLICATIONS FOR THE TREATMENT OF PSYCHOSTIMULANT DEPENDENCE

To date, studies have indicated the efficacy of mGluR7 activation in inhibiting drug taking and drug seeking of the psychostimulant drugs cocaine and nicotine. Importantly, the activation of mGluR7 is far more potent in modulating reinforcement, motivation, and seeking for psychostimulant drugs than for natural reinforcers, such as sucrose pellets. Notably, however, this conclusion is based primarily on data derived from just one compound from one chemical class. Therefore, it is important to assess whether such effects generalize to other mGluR7 agonists from different chemical classes. Nevertheless, other studies, primarily of anxiety- and antidepressant-like activity in rodent models, have used more selective ligands (e.g., ADX71743 and XAP044) and genetic manipulations (e.g., knockout mice and gene downregulation) in addition to AMN082 and MMPIP. Considering the off-target effects produced by the metabolites of AMN082, using diverse manipulations is necessary to confirm the role of mGluR7 in psychostimulant dependence and clarify the potential undesirable side-effects produced by the activation of these receptors. Such manipulations may be pharmacological or genetic, and may involve more selective ligands

than those used so far. Furthermore, AMN082 induces long-lasting internalization of mGluR7, indicating receptor desensitization and suggesting that rapid tolerance may develop when this compound is administered chronically. Therefore, to advance our understanding of mGluR7 function and its therapeutic potential as a target for the treatment of psychostimulant dependence and other psychiatric disorders, developing highly selective mGluR7 ligands is greatly needed.

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Biography

Athina Markou

LIST OF ABBREVIATIONS

AMN082	<i>N,N'</i> -Dibenzhydriethane-1,2-Diamine Dihydrochloride
AMPA	α -Amino-3-Hydroxy-5-Methyl-4-Isoxale Propionate
cAMP	Cyclic Adenosine Monophosphate
FDA	Food and Drug Administration
FR	Fixed Ratio
GABA	γ -Aminobutyric Acid
GTPγS	Guanosine 5'- <i>O</i> -[γ -thio]Triphosphate
ICSS	Intracranial Self-Stimulation
mGluR	Metabotropic Glutamate Receptor
MMPIP	6-[4-Methoxyphenyl]-5-Methyl-3-Pyridin-4-Ylisoxazolo[4,5- <i>c</i>]Pyridin-4[5 <i>H</i>]-One
NAc	Nucleus Accumbens
nAChRs	Nicotinic Acetylcholine Receptors
NMDA	<i>N</i> -Methyl-D-Aspartate
PR	Progressive Ratio

VP	Ventral Pallidum
VTa	Ventral Tegmental Area

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