Recent Advances in mGluR5 Receptor Ligands as Potential Treatments for Drug Addiction

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Abstract: - Almost a decade has elapsed since the first evidence indicating a role for mGluR5 receptors in regulating the self-administration of drugs of abuse was published. In these initial findings by Chiamulera and colleagues, mice lacking functional mGluR5 receptors did not self-administer cocaine and were indifferent to its locomotor stimulant effects. Since then, numerous pharmacological have confirmed that blockade of mGluR5 receptors reducing the rewarding and reinforcing effects of most drugs of abuse, and can reduce relapse-like behaviors (i.e., reinstatement). However, there is evidence to suggest that mGluR5 receptor antagonists impair brain reward system function and may cause deficits in learning and memory. Nonetheless, recent clinical trials with mGluR5 receptor antagonists and negative positive allosteric modulators have shown that these compounds do not cause major adverse side effects in humans. Enhancement of mGluR5 receptor function, on the other hand, with positive allosteric modulators has been proposed as a novel mechanism by which to indirectly increase NMDA receptor function, and thereby alleviate some of the cognitive deficits associated with schizophrenia. These compounds also have cognition-enhancing properties and are able to facilitate the extinction of drug-related contextual memories and drug-seeking behavior. Thus, while pharmacological compounds that decrease mGluR5 receptor function may be of use in curbing on-going drug use or reducing the risk of relapse, compounds that increase mGluR5 function may facilitate extinction learning and increase the efficacy of cue exposure therapy in reducing the salience of drug-associated stimuli.

Key Words: - glutamate, metabotropic receptor, mGluR5, addiction, drugs of abuse, extinction, self-administration, reinstatement

1 Introduction
Glutamate is the most abundant excitatory neurotransmitter in the central nervous system and governs many physiological processes including fast and slow excitatory neurotransmission, neuronal excitability, and synaptic plasticity. Glutamate receptors fall into one of two categories: ionotropic glutamate receptors, which are ligand-gated ion channels such as the NMDA, AMPA and kainate receptor subtypes that mediate fast excitatory neurotransmission, and metabotropic glutamate receptors (mGlurRs), which are G-protein coupled receptors that mediate slower, modulatory neurotransmission. To date, eight different mGlurR receptor subtypes have been cloned and characterized, and these receptors appear to have diverse neuroanatomical distributions as well as unique pharmacological and intracellular signaling properties. The Group I family of mGlurRs consists of mGlur1 and mGlur5 receptors, whereas the Group II family consists of mGlur2 and mGlur3 receptors. The Group III family consists of mGlur4, mGlur6, mGlur7 and mGlur8 receptors. With regards to experimental models of drug addiction, most research has focused on the effects of Group I and Group II mGlurR ligands [1-2]. In addition to drug addiction, such ligands have shown potential therapeutic efficacy for the treatment of other CNS disorders including chronic pain, migraine, Parkinson’s disease, depression, epilepsy Fragile X syndrome, anxiety, neurodegeneration, and gastroesophageal reflux disease [3-9].

The neuroanatomical localization of Group I mGlurRs show relatively complementary patterns of expression. High levels of mGlur1 expression are found in the olfactory bulb, thalamus, hippocampus (excluding the CA1 region), lateral septum, superior colliculus and cerebellum. Moderate levels are found in the dorsal striatum, hypothalamus, pallidum, ventral midbrain, and cerebral cortex, and low levels are observed in the amygdala, medial septum, nucleus accumbens and brainstem. In
contrast, high levels of mGluR5 expression are found in the olfactory bulb and tubercle, dorsal striatum, nucleus accumbens, lateral septum, hippocampal formation (CA1-CA3 regions and dentate gyrus), and inferior colliculus. More moderate levels of mGluR5 expression are observed in the cerebral cortex, amygdala and caudal portions of the spinal trigeminal nucleus, and mGluR5 receptor expression is low or absent in regions of the hypothalamus, medial septum, and the majority of the brainstem and cerebellum.

Most mGluR1 and mGluR5 receptors are localized postsynaptically on the perisynaptic annulus of dendritic spines. A small percentage of these receptors are localized on axon terminals in regions such as the hippocampus and cerebral cortex. Group I mGluRs, particularly mGluR5, can also be found on glial cells such as astrocytes.

2 mGluR5 Antagonists and Addiction

The first study demonstrating a role for mGluR5 receptors in addiction-related behaviors was published by Chiamulera and colleagues in 2001 [10]. In this seminal paper, the authors showed that mice carrying a targeted deletion of the mGluR5 receptor gene did not intravenously self-administer a range of doses of cocaine and showed no hyperactivity following acute administration of cocaine at doses as high as 40 mg/kg. The failure of these mice to acquire intravenous cocaine self-administration could not be attributed to a deficit in instrumental learning, as the ability of mGluR5 deficient mice to perform an operant task to receive food reinforcement was intact. The authors also showed that administration of the mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP) dose-dependently attenuated cocaine self-administration in wildtype mice. These findings represented a critical breakthrough in defining a role for mGluRs in addiction-related behaviors.

Since the landmark study by Chiamulera and colleagues, a host of other studies have been published showing that pharmacological blockade of mGluR5 receptors with MPEP or the more potent and selective antagonist 3-((2-methyl-1,3-thiazol-4-yl)ethynyl)pyridine (MTEP) reduces the self-administration of other drugs including nicotine, alcohol, methamphetamine, and heroin (reviewed in [2]; see also [11-13]). These compounds also attenuate the reinforcing efficacy of drugs of abuse as assessed by the progressive ratio paradigm. In addition, mGluR5 antagonists have been shown to attenuate the reinstatement of drug-seeking behavior produced by drug priming or presentation of drug-associated cues. Thus, it has been widely speculated that mGluR5 antagonists may represent a novel class of medications that may curb on-going drug self-administration and/or prevent relapse in human drug addicts.

The ability of mGluR5 antagonists to attenuate drug self-administration and relapse appears to be mediated, at least in part, by inhibition of mGluR5 receptor function in the nucleus accumbens. This key reward- and motivation-related forebrain region contains high levels of mGluR5 receptors, and it has been demonstrated that local infusions of mGluR5 antagonists into this region attenuate alcohol self-administration [14-15] and reinstatement of cocaine-seeking behavior [13, 16]. However, studies on the involvement of other regions of the brain in mediating the anti-addictive effects of mGluR5 antagonists are generally lacking.

Although these exciting findings suggest that mGluR5 receptors may represent as a novel pharmacological target for treating addiction, other preclinical studies have shown that mGluR5 antagonists, particularly at higher doses, may possess unwanted side effects such as amnesia. For example, MPEP and MTEP have been shown to produce deficits in learning and memory in some, but not all, behavioral paradigms [17-18]. These potential amnestic effects of mGluR5 antagonists likely arise as a result of indirect inhibition of NMDA-dependent synaptic plasticity, since mGluR5 receptors are positively coupled to NMDA receptor function. Also, MPEP has been shown to impair brain reward circuit function, as indicated by its ability to produce elevations in intracranial self-stimulation thresholds [19]. This phenomenon may contribute to the ability of mGluR5 antagonists to reduce drug self-administration.

However, the results of Phase I and II clinical trials on two compounds that selectively inhibit the function of mGluR5 receptors, fenobam (1-(3-chlorophenyl)-3-(3-methyl-5-oxo-4H-imidazol-2-yl)urea) and ADX10059, have recently been published. A small open-label clinical trial examining the efficacy of fenobam in reducing cognitive and behavioral aspects of Fragile X syndrome, showed few adverse side effects, with mild sedation being reported in 4 of 12 subjects [20]. In addition, ADX10059, a negative allosteric modulator (NAM) of mGluR5 receptor function that is currently being tested for efficacy in the treatment gastroesophageal
reflux disease and migraine, also proved to be effective for its intended indication and was reported to be generally well tolerated [21]. Mild side effects such as dizziness were reported in 9 of 12 patients, but these symptoms resolved following the first 1 or 2 doses. Another mGluR5 NAM, ADX48621, is currently in clinical trials for the alleviation of levodopa-induced dyskinesias in Parkinson’s disease. The apparent efficacy and tolerability of mGluR5 antagonists and NAMs in these human trials give hope to the idea that such compounds may eventually be of use in the treatment of addiction.

3 mGluR5 Positive Allosteric Modulators and Addiction

While nearly a decade of research has focused on inhibition of mGluR5 receptor function as a potential novel avenue for pharmacological treatment of drug addiction and alcoholism, recent attention has been turned towards positive allosteric modulators (PAMs) of mGluR5 function. The first systematically active mGluR5 PAMs to be characterized were 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB) and (S)-(4-fluorophenyl)-(3-[3-(4-fluoro-phenyl)-[1,2,4]-oxadiazol-5-yl]piperidin-1-yl) methanone (ADX47273) [22-24]. These compounds were originally designed to indirectly enhance NMDA receptor function via the positive coupling of mGluR5 receptor function to NMDA receptor activity, and thereby alleviate some of the cognitive deficits associated with schizophrenia [25]. The mGluR5 PAM ADX63365 is currently nearing entry into Phase I clinical trials for the treatment of this psychiatric disorder.

While both CDPPB and ADX47273 show antipsychotic-like activity in preclinical models [22-24], it has also been demonstrated that these compounds may also have cognition enhancing properties in normal subjects. For example, we have shown that the mGluR5 PAM VU-29 facilitates electrophysiological hallmarks of synaptic plasticity including long-term potentiation and long-term depression of synaptic function in the hippocampus [26]. In this same study, we also demonstrated that CDPPB and ADX47273 enhanced spatial learning abilities in the Morris water maze. Liu and colleagues reported that ADX47273 also has cognition enhancing effects in the novel object recognition and 5-choice serial reaction time tasks [24]. Since drug addicts often suffer from cognitive deficits such as poor decision-making, impulse control, and emotional dysregulation, it is possible that mGluR5 PAMs maybe of potential benefit in alleviating the cognitive deficits that accompany chronic drug use.

Consistent with the cognitive enhancing properties of mGluR5 PAMs, recent studies from our laboratory have shown that CDPPB facilitates the extinction of a cocaine conditioned place preference [27] and reduces extinction responding in rats following intravenous self-administration of cocaine or heroin [28]. Since extinction of maladaptive behaviors such as drug-seeking is a process of new learning, mGluR5 PAMs may be of potential use in conjunction with cue exposure therapy to reduce drug-elicted cue reactivity and craving.

4 Conclusion

Pharmacological alteration of mGluR5 receptor function has been, and continues to be, an area of exploration for the development of novel therapies to aid in the treatment of drug addiction and other CNS disorders. Animal studies suggest that inhibition of mGluR5 receptor function may attenuate on-going drug use and/or reduce the ability of acute drug exposure or drug-associated cues to reinstate drug-seeking behavior. However, if approved by the Food and Drug Administration, the use of such compounds will likely need to be exercised with caution, as unwanted side effects such as amnesia or dizziness may appear with higher doses. Conversely, allosteric enhancement of mGluR5 function may and facilitate extinction learning during cue exposure therapy.

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