

# Group I Metabotropic Glutamate Receptors: Involvement in Drug-Seeking and Drug-Induced Plasticity

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**Abstract:** L-glutamate is the principal excitatory neurotransmitter at fast synapses in the mammalian central nervous system, and signals through a number of ionotropic and metabotropic receptors. Among the latter are the group I metabotropic glutamate (mGlu1 and mGlu5) receptors that upon activation elevate intracellular calcium levels through activation of the phospholipase C pathway. The role of glutamatergic transmission in both the development of addiction and the phenomenon of relapse that may occur after prolonged abstinence, has come under intense scrutiny in recent times. While both mGlu1 and mGlu5 receptors have been implicated in certain aspects of the addictive state, the exact roles these receptors play in this process is, as yet, unclear. This review will introduce contemporary theories on drug addiction, including neural circuitry, before critically assessing the current body of knowledge on group I metabotropic glutamate receptors in this regard. This will involve an in-depth discussion of the distribution of these receptors in the brain, their presence in neural pathways known or postulated to be involved in addiction and their involvement in drug-related behavioral paradigms. The effect of acute and chronic drug administration on the activity and expression of group I metabotropic glutamate receptors will be investigated, as will the effect these receptors have on behavioral and biochemical responses to drugs of abuse. Finally, there will be a brief discussion on current and future therapeutic applications using our knowledge of these receptors, and the direction that future studies will need to take to close the gaps in our understanding.

**Keywords:** Metabotropic glutamate receptor, reward, motivation, dependence, addiction, ethanol, cocaine.

## INTRODUCTION

### Addiction in Society

Addiction to drugs of abuse is a leading health problem in Western society. In a survey conducted in 2006, the U.S. Department of Health and Human Services estimated that the prevalence of substance use disorders amongst the general population was approximately 9.2% [1]. The cost of drug addiction to individual addicts and their family and friends is obvious, but there are also significant economic and social burdens on the community. Associated problems such as loss of productivity, disease spread through infected needles, traffic accidents, domestic violence and drug-related crime are an intrinsic part of the overall problem. It has been estimated that drug addiction can cost up to 3.5% of gross domestic product (GDP) in Western countries [2]. In perspective, the estimated GDP of the United States in 2007 was US\$13.86 trillion, and 3.5% of this figure is approximately \$485 billion [3]. However, research into addiction currently receives less than 2% of the public and private funding of cancer research, despite being a medical problem of similar magnitude and having a greater market potential for therapeutics [2]. As a consequence, our knowledge of addiction has not progressed as quickly as other, perhaps more socially acceptable, diseases.

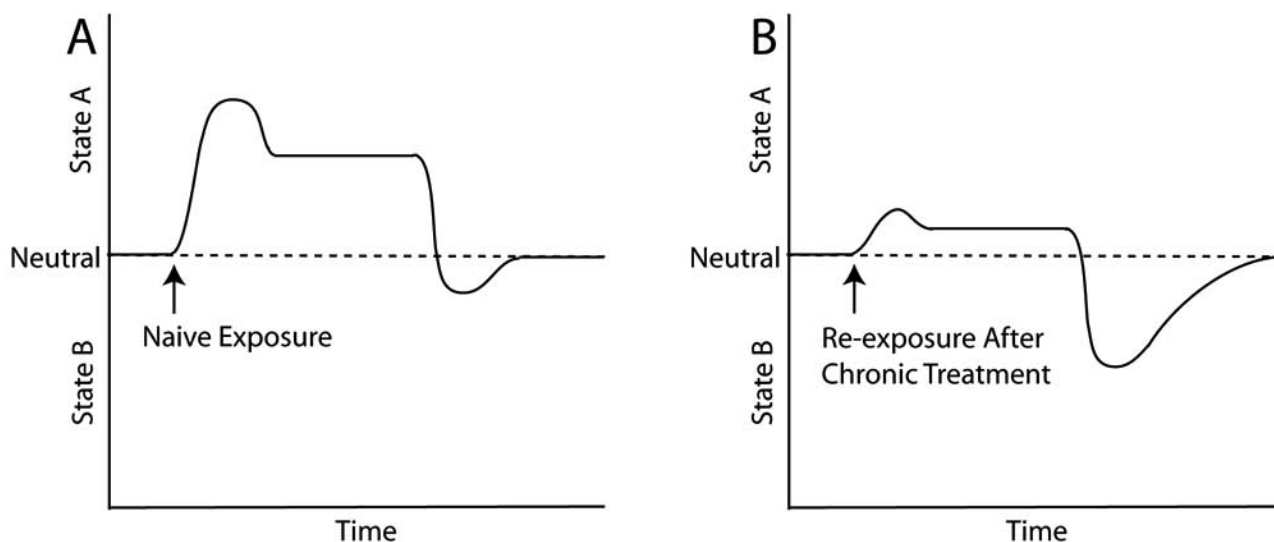
Broadly defined, addiction is the loss of control over drug use, including compulsive drug-seeking and drug-taking behaviors that continue despite significant negative consequences and/or reductions in drug efficacy [4]. While a desire to elevate mood or alleviate stress may initiate drug use, the development of addiction is more complex than simply being unwilling to cease drug taking due to the desire to experience hedonic effects. One of the driving questions behind addiction research is what factors, be they neurological or sociological, predispose an individual to progress from casual to compulsive drug use.

### Theories of Addiction

In a number of reviews, the concept of “hedonic dysregulation” and “allostasis” of a reward system of the brain has been posited to

underpin the development of addiction [5-7]. According to this theory, the initial motivation behind drug use is a desire to experience positively reinforcing acute effects, while in the addicted state the main motivation for drug-seeking is the need to alleviate an unpleasant withdrawal state and/or abstinence-related dysphoria. The neural basis for this theory lies in drug-induced neuroadaptations in the brain reward system. The term “allostasis” is used to describe a situation where the maintenance of stable physiological conditions (set point) is maintained outside the normal homeostatic range. As a consequence, when the body returns to the *homeostatic* set point in the absence of drug (i.e. withdrawal), it is not within the range of the new *allostatic* set point. This results in unpleasant symptoms in the absence of the drug and ergo drug-seeking behavior during withdrawal, as the body requires the drug to return within allostatic bounds. Thus, in the addicted state, a self-perpetuating cycle traps the individual in a situation where the main goal becomes attaining the drug to alleviate negative withdrawal symptoms, and further drug use pushes the allostatic state even further away from true homeostasis. Essentially, this theory provides a neural explanation for the long-established psychological model of addiction known as the “opponent-process” theory [8, 9]. Although intended to be applied to all forms of acquired motivation, it has particular relevance to the process of drug addiction. There are two distinct phases in this model, each of which describes the hedonic state of the individual in question. Using acute administration of an opiate as an example, “State A” represents the positive emotions experienced during the period when the drug effect is present, while “State B” occurs once the drug effect has dissipated and may represent negative reinforcement that occurs due to the absence of State A (thus opponent-process). It is proposed that after repeated stimulations, changes occur in the hedonic responses of the subject during these two phases, Fig. (1). To continue with the opiate analogy, upon initial exposure State A is a period of intense euphoria (rush) followed by a slightly more stable feeling of pleasure. State B follows when the drug effect has diminished, resulting in a brief period of craving and withdrawal symptoms before a return to normalcy. However, after multiple stimulations with the opiate, State A is no longer a period of euphoria, but one more akin to relief. Correspondingly, the cravings or post-dependent dysphoria encountered in State B are now far more intense and prolonged and may represent a post-dependent dysphoric state. Moreover, there is evidence that after discontinuation of chronic drug use, the cravings of State B actually increase rather than abate as the period of absti-

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**Fig. (1).** Schematic diagrams illustrating the opponent-process model of addiction. **A:** Hedonic response after initial exposure to a stimulus (eg. drug administration) **B:** Response to re-exposure after repeated stimulation. State A represents the positively reinforcing phase after a stimulus, while State B represents the negatively reinforcing effects that follow. Note that the acute euphoria present after naïve exposure is absent after repeated exposure, while in contrast, the negatively reinforcing phase is exaggerated. Modified from [9].

nence increases, a phenomenon referred to as “incubation of craving”, and one that has clear relevance to the propensity to relapse in addicts [10].

Another mainstream theory of addiction is referred to as the incentive-sensitization hypothesis [11-15]. This theory posits that the primary motivation behind the compulsive drug-seeking and taking behaviors associated with addiction is neither a desire for pleasurable acute effects nor a desire to alleviate negative withdrawal symptoms. Rather, the neuroadaptations caused by drugs of abuse render the brain hypersensitive (“sensitized”) to drug effects and drug-associated stimuli. However, the neural systems sensitized are not necessarily only those involved in mediating the pleasurable effects of the drug (distinct from the allostasis theory discussed previously). Instead, there is sensitization of the incentive-salience (motivational power) attributed to the drug and drug-associated cues, and it is this phenomenon that causes compulsive drug-seeking and the susceptibility to relapse.

It is important to note that both the allostasis and incentive-sensitization theories agree on two key points; a) drugs of abuse are able to cause stable neuroadaptive changes in the brain and b) among the systems influenced are those normally associated with natural reward (namely, the mesolimbic dopamine system). The mesolimbic dopamine system comprises dopaminergic neurons that project from the ventral tegmental area (VTA) to limbic structures in the forebrain (nucleus accumbens (NAc), caudate putamen (CPu), amygdala and prefrontal cortex (PFC)). Every drug of abuse is able in one way or another to activate this system, increasing firing in the VTA which in turn increases extracellular dopamine levels in forebrain structures [16]. It is at this point that we introduce another hypothesis that will be commented upon in this review, which posits that drug addiction may be considered as a pathological form of natural learning and memory [17-19]. This theory stems from the seminal work by Ramon y Cajal in which he suggested that alterations in the synaptic connections between neurons in the brain are involved in data storage [20]. Long-term potentiation (LTP) is the term now applied to an activity-dependent strengthening of synaptic transmission, while long-term depression (LTD) refers to a weakening of synaptic transmission [21]. Collectively, these changes are known as synaptic plasticity, referring to activity-dependent alterations in the morphological and functional properties of a neuron or neural network. These two phenomena are

now known to be critically involved in learning and memory processes, as well as a number of other functions [22].

More recently, it has been proposed that synaptic plasticity also occurs in the mesolimbic dopamine system after exposure to drugs of abuse, and plays a critical role in the development of drug addiction [23]. For example, repeated cocaine administration results in long term anatomical and neurochemical changes in neurotransmitter pathways [24], and even after acute cocaine administration, synaptic plasticity was observed in the VTA, but not the hippocampus, indicating that specific, drug-induced neuronal adaptations had occurred [25]. Furthermore, agents that can prevent synaptic adaptation, such as the *n*-methyl-*d*-aspartate (NMDA) receptor antagonist MK-801, are able to inhibit conditioned place preference, self-administration and the development of sensitization to drugs of abuse in rodent models [26-28]. However, though the *development* of sensitization to cocaine is prevented by pre-treatment with MK-801 directly into the VTA [29], cross-sensitization to an acute (systemic) MK-801 challenge can occur in animals already sensitized to cocaine [30]. Simply put, sensitization refers to the enhancement of drug-induced locomotor effects after chronic treatment of the same drug [31], while cross-sensitization refers to the increased sensitivity to one drug (in this case MK-801) due to prior exposure to another (cocaine). This phenomenon is believed to be paralleled in humans, providing a possible reason why the transition from one illicit drug to another is made when the drug of choice becomes unavailable [12]. As regards MK-801 and cocaine, these data would suggest that NMDA receptors are involved in the synaptic plasticity caused by chronic cocaine, and that the neuroadaptations caused by cocaine result in altered glutamate transmission which can affect the response to a subsequent MK-801 challenge. Clearly, while the VTA apparently represents an anatomical substrate for the development of sensitization, the expression of these behaviors also includes other areas, such as the NAc [32-34]. It also seems that preventing plasticity in specific structures in the brain, such as the VTA, can impair the reinforcing properties of drugs of abuse, blocking both conditioned place preference and self-administration behaviors (for a review on the role of synaptic plasticity in addiction see [35]).

In addition to inducing LTP and LTD, chronic exposure to drugs of abuse induces structural adaptive alterations in medium spiny neurons of the basal ganglia. These neurons receive input

from both dopaminergic projections from the VTA which terminate upon the shafts of the spines, and glutamatergic efferents from the PFC and basolateral amygdala which terminate upon the 'heads' [36]. Chronic psychostimulant administration increased both dendritic branching and spine density in these neurons [37-39], a mechanism believed to be dependent on cyclin-dependent kinase 5 [40]. Interestingly, other drugs of abuse affect the adaptive morphology of medium spiny neurons in different ways. Morphine administration causes a decrease in both dendritic branching and spine density [41], while alcohol decreases spine density, but also causes alterations in dendritic structure, including increases in diameter and changes in orientation [42]. There is evidence indicating that drugs of abuse (cocaine, in this example) are able to elevate extracellular glutamate levels in the VTA [43, 44] as well as in the NAc through glutamatergic efferents descending from the PFC, although levels in cortex itself remain static [45-47]. These glutamatergic neurons are considered key substrates for the neuroadaptations that occur as a response to the chronic presence of drugs within the mammalian CNS [47-49]. Interestingly, the chronic pre-synaptic depression induced in corticostriatal terminals by repeated methamphetamine administration can be partially reinstated by re-exposure to the drug ten days into withdrawal [50]. This "renormalisation" provides further evidence for a synaptic basis for drug relapse in humans.

### Distribution and Physiology of Group I mGlu Receptors

L-glutamate is the major excitatory neurotransmitter in the mammalian CNS, and elicits physiological effects by activation of both ionotropic [NMDA,  $\alpha$ -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) and 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine (Kainate)] and metabotropic (mGlu1-8) receptors [51]. Evidence for the existence of a metabotropic receptor for endogenous glutamate was first reported in 1985, when it was found that inositol phosphate formation was induced by glutamate in striatal neurons [52], and soon after the presence of a new type of glutamate receptor that activated regulatory G-proteins was confirmed [53]. The first of these receptors was characterised in 1991, and seven other receptors were discovered in the next few years [54-60]. This family of metabotropic glutamate receptors is currently divided into three groups, based on pharmacology, sequence homology and receptor coupling. Upon activation, group I (mGlu1 and 5) receptors elevate intracellular calcium levels by coupling to  $G_q/G_{11}$  proteins, which in turn activate the phospholipase C (PLC) pathway. Group II (mGlu2 and 3) and Group III (mGlu4, 6, 7 and 8) receptors typically couple through  $G_i/G_o$  proteins and reduce cyclic AMP levels *via* inhibition of adenylate cyclase [61].

However, this description of physiological signalling, at least concerning the group I mGlu receptors, is grossly over-simplified. Members of this group form functional heterodimers *in vivo* with calcium sensing receptors [62], adenosine  $A_{2A}$  receptors [63] and  $A_1$  receptors [64] and transactivate epidermal growth factor (EGF) receptors, which influences extracellular-regulated kinase (ERK)2 signalling [65]. Activation of these receptors also modulate  $\gamma$ -aminobutyric acid (GABA) $_A$  receptor function [66] as well as ERK1 and cannabinoid signaling, in that activation of post-synaptic mGlu1/5 receptors is required for LTD mediated by cannabinoid 1 (CB $_1$ ) receptors [67-69]. In addition, mGlu1 and mGlu5 receptors are functionally linked to NMDA receptors through a series of scaffolding proteins including Homer [70, 71]. Finally, group I mGlu receptors are able to signal through pathways independent of their respective G-proteins, in that excitatory post-synaptic currents mediated by mGlu1 in the pyramidal cells of the CA3 area of the rat hippocampus appear to be mediated through a Src family protein kinase [72]. The fact that group I mGlu receptors have such a wide

influence over intracellular signalling pathways has made it difficult for researchers to pinpoint which pathway(s) are influenced by receptor modulation.

Group I mGlu receptors are located both post-synaptically [73-75], where they act to modulate neuronal excitability and potentiate NMDA receptor currents [76, 77], and pre-synaptically, where they appear to be involved in inhibiting excitatory transmitter release [78]. However, it appears that the inhibitory role of pre-synaptically located receptors may be structure-dependent, as while there is evidence for release inhibition in the hippocampus, administration of the group I mGlu agonist (RS)-3,5-dihydroxyphenylglycine (DHPG) in the NAc increased extracellular glutamate levels [79]. Recent data also show that group I mGlu receptors can facilitate glutamate release from mouse cortical synaptosomes [80]. Interestingly, mGlu1 and mGlu5 appear to be distributed in an almost reciprocal manner; in regions where mGlu1 is richly expressed, mGlu5 is present at much lower levels, and vice versa [81, 82]. mGlu5 is densely expressed in limbic and cortical structures, including the NAc, CPu and PFC, supporting a potential physiological role in learning and memory and a possible pathological role in addiction [55]. mGlu1 is weakly expressed in cortical areas and the basal ganglia, but is present at much higher levels in the hypothalamus, thalamus and the CA3 region and dentate gyrus of the hippocampus [83]. Pharmacological activation of group I mGlu receptors facilitates dopamine release in rat striatum *in vivo* [84], and when activated in the VTA both mGlu1 and mGlu5 facilitate dopamine release in the medial PFC [85]. In addition, systemic administration of mGlu5 agonists could also modulate the dopamine transporter (DAT) in terminal fields, which is responsible for the reuptake (clearance) of dopamine from the synaptic cleft. Activation of mGlu5 resulted in a decrease in the efficiency and capacity of DAT in rat striatal synaptosomes, which would cause an increase in extracellular dopamine levels if replicated *in vivo* [86].

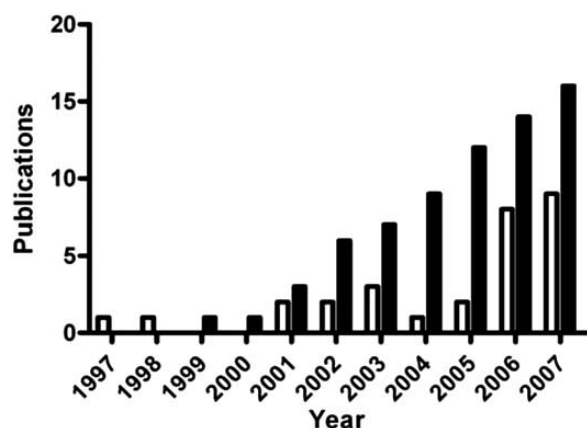
It is the intent of this review to critically examine the literature to date linking group I mGlu receptors with drug abuse and/or addiction. This will involve systematically examining the lines of evidence that link mGlu1 and/or mGlu5 to psychostimulant, ethanol, nicotine and opiate reward and plasticity.

### METABOTROPIC GLUTAMATE RECEPTORS AND DRUGS OF ABUSE

Research into the role of the group I mGlu receptors in response to drugs of abuse has gathered momentum in recent years, although the body of literature on mGlu5 remains far more extensive than mGlu1, Fig. (2). This bias toward mGlu5 is likely due to the distribution of the two receptor subtypes throughout the brain; however, as both are very similar not only in signalling and pharmacology, but also in influencing other receptors, research into mGlu1 has also intensified over the past few years.

#### Psychostimulants

One source for the strong interest in the role of mGlu5 in behavioral responses to drugs of abuse was a study in 2001 that reported that an intraperitoneal injection of cocaine failed to induce locomotor stimulation in mGlu5-deficient mice, and that these mice also did not self-administer cocaine [87]. In addition, this study provided evidence that this was a drug-specific effect, as there appeared to be no deficiency in responding for food under an operant schedule. These data would suggest that while mGlu5 deficiency does not alter motivation for natural reward, it does appear to influence the motivation to acquire cocaine. This observation may implicate mGlu5 in being differentially involved in the effects of cocaine and natural reward on plasticity in the reward pathway. Indeed, a recent study found persistent LTP in the VTA that was present three weeks after cessation of cocaine self-administration,



**Fig. (2).** Graph showing the number of publications over the past 10 years on mGlu1 (open bars) and mGlu5 (closed bars) receptors with regard to drug addiction. mGlu1 trend was compiled by searching the PubMed database for ("*metabotropic glutamate receptor 1*" OR *mGlu1* OR *mGluR1* OR *Grm1*) AND (*addiction* OR *drug abuse* OR *dependence* OR *motivation*) and limiting by year. Same formula was used for mGlu5 with the exception that the number 1 was replaced by 5.

while the enhancement of glutamatergic signaling as a result of sucrose self-administration was far more transient in nature [88]. This interest has been maintained to the present, resulting in a vast body of literature on the role of this receptor with regard to psychostimulant-induced behaviors (particularly cocaine, summarised in Table 1).

Although not yet fully elucidated, there is clearly a role for mGlu5 in the acute effects of cocaine. Perhaps more interesting from a clinical perspective however, mGlu5 also appears to play a critical role in the long-term neuroadaptations associated with chronic exposure. Researchers have reported that repeated cocaine treatment in rats results in an increase of mGlu5 receptor expression in the NAc [89] and hippocampus [90], while chronic exposure to cocaine is able to reduce mGlu5-dependent LTD [69]. Moreover, repeated cocaine administration disrupts the ability of the group I mGlu receptor agonist DHPG to induce glutamate release in the

NAc three weeks after the cessation of cocaine administration [79]. Another important insight into the role of mGlu5 in regard to chronic cocaine administration is that cue-induced reinstatement after extinction in rats is attenuated by administration of either 6-methyl-2-(phenylethynyl)pyridine (MPEP), a relatively selective mGlu5 antagonist [91], or 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP), a more selective analogue of MPEP [92]. These findings are supported by a study in primates which showed MPEP attenuated both cocaine self-administration and drug-primed reinstatement of cocaine-seeking [93]. These data suggest that mGlu5 appears to be involved in not only the motivational and reinforcing properties of the cocaine, but also in attributing salience to drug-paired cues.

Another line of evidence linking the group I mGlu receptors with behavioral responses to cocaine lies in their relationship with Homer proteins. As mentioned earlier, Homer is a part of the protein scaffold between mGlu1/5 and NMDA receptors. Homer1b/c levels are attenuated in the NAc of rats in withdrawal from chronic cocaine exposure [79], while an engineered reduction in Homer1 expression in the NAc results in a sensitized state similar to that observed during withdrawal [94]. Moreover, deficiency in either Homer1 or Homer2 isoforms results in a sensitized behavioral state in mice [95]. This means that upon naïve exposure to cocaine, Homer deficient mice behave as though they have previously been chronically exposed (eg. exaggerated locomotor activity compared to wild type). Finally, an extensive study of both rats and mice has shown that repeated cocaine administration results in structure-dependent plasticity in the mammalian brain. Homer1 and 2 were both down-regulated by cocaine treatment in the NAc shell and hippocampus, which was accompanied by a decrease in mGlu1 expression in these areas. In the PFC, however, chronic cocaine exposure resulted in an upregulation in Homer2 and mGlu1 without any significant impact on Homer1 [96].

Acute administration of amphetamine induces immediate early gene (IEG) expression in the rat striatum through an mGlu5-dependent mechanism(s) [103, 104], which in turn appears to be dependent on protein kinase C (PKC) and NMDA receptors [105]. Pre-treatment with MPEP attenuates the acute hyperlocomotor effects of amphetamine in rats [106], while the development of behavioral sensitization to chronic amphetamine is unaffected by MPEP treatment [107], despite solid evidence for the involvement of mGlu5 in NMDA receptor currents in medium spiny neurons [108]. This would suggest that mGlu5 is not critical for the synaptic

**Table 1.** Summary of the Effects of mGlu5 Negative Modulation on Cocaine-Related Behaviors in Rodent Models. Reinstatement Section Represents Studies that Investigated Cue-Induced Reinstatement to Cocaine Seeking after Extinction. MPEP: the Antagonist 6-methyl-2-(phenylethynyl)pyridine; MTEP: the antagonist [(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine

	Rat	Mouse
Conditioned Place Preference	No effect MPEP [97]	Attenuated MPEP [98]
Acute Locomotion	Attenuated MPEP [97] No effect MTEP [99]	Attenuated MPEP [98] Knock-out [87]
Behavioral Sensitization Development/Expression	No effect MPEP [97] (Development) MTEP [99] (Expression)	N/A
Self-Administration	Attenuated MPEP [100-102]	Attenuated Knock-out [87] MPEP [87]
Reinstatement	Attenuated MPEP [91] MTEP [92]	N/A

plasticity that is causally linked to a sensitized behavioral state. Interestingly, there is a concurrent reduction in mGlu5 receptor mRNA expression in the NAc and CPU during the expression of behavioral sensitization to amphetamine, a phenomenon which persists at least 28 days into withdrawal [109]. This study provides a contrast to an aforementioned study of cocaine which found an increase in mGlu5 mRNA levels in these structures after repeated administration [89]. This apparent discrepancy may be due to a number of factors, including the difference in the mechanism of action between the two drugs (cocaine inhibits neurotransmitter reuptake, amphetamine causes neurotransmitter release [110]), or the methodology used in each experiment (Wistar vs. Sprague-Dawley rats, difference in the timeframes examined). Amphetamine administration has also been shown to influence mGlu5 receptor expression in the developing rat in a number of brain structures [111], as well as increasing the expression and signalling capacity of mGlu5 receptors in hippocampal cell cultures [112, 113]. In contrast, a recent study found that while mGlu5 receptor expression in the rat striatum was unchanged after behavioral sensitization to amphetamine, associated proteins such as PLC and  $G\alpha_{q/11}$  were up-regulated [114]. This may suggest that psychostimulant-induced changes in mGlu5 receptor expression are more transient than the influence on downstream transduction elements, or that there are influences on transduction proteins that, while susceptible to amphetamine, are independent of mGlu5.

Evidence from recent studies indicated that mGlu1 may also play a role in drug-induced behaviors. Administration of the selective mGlu5 antagonist [(2-methyl-1,3-thiazol-4-yl)ethyl]pyridine (MTEP) had no effect on the expression of cocaine sensitization, while mGlu1 blockade by (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate (EMQMCM) attenuated expression of sensitized behavior in rats [99]. mRNA expression for both group I mGlu receptors remained unaltered in the CPU or NAc after acute amphetamine administration. However, after chronic treatment, mGlu1 levels were increased in both structures 3 hours after final amphetamine exposure, but there was no difference from control animals in the long term (up to 28 days). Conversely, 3 hours after final exposure, mGlu5 was markedly reduced in both structures, an alteration that was maintained up to 28 days into the withdrawal period [109]. In theory, this means that a reduction in mGlu5 receptor expression may contribute toward the post-dependent dysphoric state or the incubation of craving. It also appears that mGlu1-deficient mice display an exaggerated locomotor response to amphetamine administration compared to wild type littermates [115].

## Ethanol

There have been numerous studies that provide strong links between mGlu5 and ethanol-related behaviors [116], and a recent study has even marked variation in the mGlu5 gene as an indicator for predisposition to develop dependence to alcohol in humans [117]. Among the physiological actions of ethanol is the ability to directly inhibit NMDA receptors, which are functionally linked to group I mGlu receptors [118]. As with cocaine, the importance of Homer in ethanol-induced plasticity has become apparent, providing another link between mGlu1/5 and ethanol related behaviors [119]. However, like the structure-specific alterations observed with chronic exposure to cocaine, there seems to be a similar regional specificity observed with ethanol. Chronic exposure to ethanol in mice results in an up-regulation of Homer2 and mGlu1 levels in the NAc, which is maintained (after cessation of ethanol access) for at least 2 weeks for mGlu1, and 2 months for Homer2 [120]. Other studies have shown that chronic ethanol exposure reduced mRNA expression of mGlu1 in the cerebellum and CA3 region of the hippocampus, while mGlu5 message was reduced in the dentate gyrus and CA3 [121, 122].

Activation of mGlu5 results in phosphorylation of PKC through a phospholipase C-dependent pathway [123], and PKC is also capable of modulating mGlu5 activity [124]. There is now a large body of evidence demonstrating that ethanol is able to inhibit mGlu5 activity through activation of PKC [125-127]; particularly the PKC $\epsilon$  variant. Mice deficient in PKC $\epsilon$  drank less ethanol and were more sensitive to ethanol-induced hypnosis, while conditional rescue of PKC $\epsilon^{-/-}$  mice restored these behaviors [128, 129]. The reduced consumption and increased sensitivity to ethanol have been replicated in mice lacking mGlu5 [130], and pharmacological studies showed that MPEP pre-treatment increased sensitivity to ethanol-induced hypnosis and locomotor inhibition [131]. Both aforementioned studies provide more indirect evidence that the role of mGlu5 in the effects of ethanol involves PKC $\epsilon$ . Moreover, studies with MPEP in wild type mice suggest that mGlu5 antagonism reduces ethanol consumption through a pathway regulated by PKC $\epsilon$  [132]. Although not specifically focused on the epsilon isoform, research into alcohol-induced neuropathic pain nevertheless has provided another strong link between mGlu5, PKC and alcohol. mGlu5 protein levels were induced in superficial dorsal horn of the spinal cord both immediately after chronic alcohol consumption and after withdrawal [133]. The neuropathic pain attributed to chronic ethanol exposure was attenuated by treating the rats with either MPEP or the specific PKC inhibitor (S)-2,6-diamino-N-[[1-(oxotridecyl)-2-piperidinyl]methyl] hexanamide dihydrochloride (NPC15437; [134]).

mGlu5 has been extensively investigated with regard to ethanol-related behaviors, particularly in operant paradigms in which rodents are required to perform an instrumental task for access to ethanol (summarised in Table 2). Work in conditioned place preference paradigms have yielded conflicting results, with one study finding no effect of MPEP (1, 5 or 20mg/kg) on ethanol-induced place preference [98], while another observed a significant attenuation using a different dose of the same antagonist (10mg/kg) [116]. While the differences observed may have been due simply to the use of different mouse strains (DBA/2J and C57BL/6J), there is also likely to be an involvement of the pharmacokinetic properties of MPEP and/or ethanol. The former study did not observe any effect, even at a high dose of MPEP when administered 10 min prior to a 5 min conditioning session, while a significant attenuation was observed when a moderate dose was administered 30 min prior to a 15 min conditioning session. Despite this discrepancy, the majority of the available literature supports a role for mGlu5 receptors in behavioral responses to ethanol, as mGlu5 antagonism with MTEP can attenuate the expression of ethanol induced sensitization in mice, a measure of ethanol-induced plasticity [135], while MPEP pre-treatment dose-dependently lowered the break point for ethanol seeking in a progressive ratio paradigm in rats [136]. Acamprostate, a pharmacological agent currently registered to treat alcohol dependence, is believed to antagonise mGlu5 receptors (not mGlu1), although the relevance of this property to the abstinence-enhancing ability of the drug has not been conclusively proven [137, 138]. During alcohol withdrawal there is enduring glutamatergic hyperactivity in the brain [139], and acamprostate may inhibit this hyperexcitability through actions at mGlu5 and NMDA receptors [140].

mGlu1 receptors have also recently been implicated in alcohol-related behaviors, in that the specific antagonist 7-(hydroxyimino)-cyclopropan[b]chromen-1-carboxylate ethyl ester (CPCCOEt) reduced instrumental responding for ethanol, free-choice ethanol drinking, ethanol-induced conditioned place preference and facilitate ethanol-induced locomotor sedation in mice [116]. However, this study contrasts with another published less than two years later, which found that a higher dose of CPCCOEt had no effect on ethanol-induced locomotion or the duration of ethanol-induced hypnosis in mice [131]. Although the same strain of mice and dose of ethanol was used in the two studies, a possible explanation for this discrepancy is that while the former study administered CPCCOEt 30 min

**Table 2. Summary of the Effects of mGlu5 Negative Modulation on Ethanol-Related Behaviors in Rodent Models. Reinstatement Section Represents Studies that Investigated Cue-Induced Reinstatement to Ethanol Seeking after Extinction. MPEP: the Antagonist 6-methyl-2-(phenylethynyl)pyridine; MTEP: the antagonist [(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine**

	Rat	Mouse
Consumption	Attenuated MTEP [141] MPEP [142, 143]	Attenuated MPEP [116, 132, 144] MTEP [145] Knock-out [130]
Seeking	Attenuated MPEP [143, 146]	Attenuated MTEP [145] MPEP [116]
Reinstatement	Attenuated MPEP [143, 146]	N/A

prior to ethanol administration and monitored the subjects for 120 min, the latter only allowed 10 min before a 60 min monitoring session, indicating there may be pharmacokinetic considerations when using CPCCOEt. A recent study in rats showed that the reduction of ethanol self-administration in rats due to administration of the mGlu1 antagonist JNJ16259685 could not be distinguished from the locomotor inhibition associated with the antagonist itself [147]. Clearly, while a role for mGlu1 receptors in ethanol related behaviors remains equivocal, more research is required to reconcile this issue.

As was mentioned earlier, group I mGlu receptors are capable of functional interaction with a number of other receptors, at least indirectly influencing numerous signalling pathways. NMDA receptors are perhaps the best example of this, as they are directly scaffolded to group I mGlu receptors, and are potentiated upon application of DHPG, a group I mGlu receptor agonist [148]. NMDA-mediated LTD is also dependent on mGlu5 [149, 150]. Furthermore, it seems that co-activation of mGlu5 and NMDA receptors results in the activation of an ERK pathway mediated by the aforementioned scaffolding proteins which is independent of NMDA calcium currents [151]. NMDA receptors have been recognised for some time as being involved in physiological responses to drugs of abuse and the process of addiction [152], and it appears incontrovertible that the group I mGlu receptors are able to modulate these receptors in this regard [153].

The other two receptors to be discussed in this section have particular relevance to the involvement of mGlu5 in ethanol-related behaviors. Because of the biphasic, dose-dependent physiological effects of ethanol [154], it seems plausible that a plethora of intracellular signalling pathways are modulated. The probability that the complexity observed in the behavioral phenotype is a reflection of a similar complexity at the cellular level has led some researchers to examine the influences of receptor interactions on downstream signalling pathways. mGlu5 receptors modulate GABA<sub>A</sub> receptor function [66], which is involved in the discriminative stimulus properties of ethanol [155]. Both receptors are co-expressed in regions of the brain implicated in behavioral responses to ethanol, and mGlu5 blockade attenuated the discriminative stimulus effect of ethanol through negative modulation of GABA<sub>A</sub> receptors [156].

Recent work has also brought into focus the relationship between mGlu5 and adenosine A<sub>2A</sub> receptors. The possibility of such a relationship was first reported in 2000, and subsequent work indicated that A<sub>2A</sub> and mGlu5 receptors form functional heterodimers *in vitro* and *in vivo* [63, 157]. Since then, a number of studies have provided evidence of a synergistic interaction between these apparently divergent receptors [158, 159], particularly in animal models of Parkinson's disease [160, 161]. A<sub>2A</sub> receptor antagonism reduces operant self-administration of ethanol in rats [162], and as men-

tioned earlier, mGlu5 antagonism has similar effects. Using the mGlu5 receptor antagonist MTEP and the A<sub>2A</sub> receptor antagonist SCH-58261, Adams and colleagues reported an apparently synergistic interaction between these two receptors with regard to ethanol self-administration and relapse-like ethanol seeking in rats. When MTEP and SCH-58261 were co-administered at doses found to be individually ineffective, a dramatic attenuation of both fixed ratio self-administration and cue-induced reinstatement following extinction was observed [163]. This implies that mGlu5 and A<sub>2A</sub> receptors may act through a common pathway to influence motivation to consume ethanol, and that concomitant negative modulation of both receptors has a greater downstream impact than blockade at either individual receptor. These findings lead to the suggestion that drug experience or the post-dependent dysphoric state may induce more significant changes in the number and/or function of heterodimers than in homodimeric complexes. Perhaps even more intriguing is that these complexes appear to play a role both in the motivation to consume ethanol (reinforcing properties) and the propensity to relapse (drug-induced plasticity). It will be of great interest to determine whether chronic exposure to ethanol and/or ethanol withdrawal can regulate such receptor interactions and whether such complexes can be quantified in human brain.

### Nicotine

While the exact role of glutamate (and thus glutamate receptors) in the positively reinforcing effects of nicotine is as yet unclear, a number of studies have set out to examine the role of mGlu5 in this regard. After three days of nicotine treatment, mRNA and protein levels for both mGlu1 and mGlu5 were upregulated in the rat amygdala, though after seven days of treatment both markers had returned to baseline. A similar pattern was observed in certain Homer isoforms, suggesting an increase in NMDA receptor interaction with the group I mGlu receptors as a result of nicotine treatment [164]. Utilising an intracranial self-stimulation paradigm in rats, Harrison and colleagues found that the reward-potentiating effects of nicotine were unaffected by administration of MPEP [165]. Interestingly, nicotine-induced LTP in the rat dentate gyrus is dependent on mGlu5, while control LTP (using high-frequency stimulus) was independent of mGlu5 [166]. There is also strong evidence for a permissive role of nicotinic acetylcholine (nACh) receptors with regard to pre-synaptic mGlu5 receptors in the hippocampus. Nicotine treatment induced noradrenaline (NA) release through actions at nACh receptors, and co-treatment with DHPG (group I mGlu agonist) resulted in exaggerated NA release when compared to nicotine alone. Furthermore, DHPG was unable to induce NA release above basal levels in the absence of nicotine. It was also shown that this effect was due to mGlu5, but not mGlu1, as the DHPG component of the noradrenaline release was blocked by MPEP, but not the specific mGlu1 antagonist CPCCOEt [167].

Nicotine self-administration studies have shown MPEP to dose-dependently reduce responding while having no effect on responding for food in both rats and mice [100, 168-170], while MPEP also attenuated both cue and drug-induced reinstatement of nicotine-seeking in rats [170, 171]. However, one study in rats reported that MPEP administration decreased the motivational properties not only of nicotine, but also of food [101]. In mouse studies however, nicotine reinforcement as assessed by conditioned place preference was unaffected by administration of MPEP [98]. Though appearing anomalous, considering MPEP reduces nicotine self-administration, these data are supported by another finding that showed MPEP, at doses that reduced self-administration of nicotine, did not appear to impact upon the facilitation of nicotine-induced brain reward [100]. It also appears that mGlu1 plays a significant role in nicotine-related behaviors, as administration of the mGlu1 antagonist EMQMCM resulted in a dose-dependent attenuation of both cue- and drug-induced reinstatement to nicotine seeking in a mouse model [172].

### Opiates

Morphine has well documented withdrawal symptoms after cessation of chronic use, and these symptoms are considered a major negative reinforcer facilitating relapse in addicts [173]. Glutamate hyperactivity may contribute to the morphine withdrawal state leading to interest in the role of mGlu receptors in this regard [174]. Using an array of behavioral markers of morphine withdrawal in rats, Rasmussen and colleagues found that both MTEP and MPEP were able to attenuate chewing, digging, salivation and weight loss at non-sedative doses [174]. mGlu5 blockade with MTEP also impaired the expression of behavioral sensitization to morphine as well as reducing the number of escape jumps, a quantifiable marker of morphine withdrawal [175]. Consistent with this interaction of mGlu5 with the effects of chronic morphine, treatment with MPEP impairs the development of tolerance to morphine-induced antinociception [176, 177]. Morphine reward, as examined by a conditioned place preference paradigm, is not affected by doses of MPEP at or lower than 20mg/kg, while a 30mg/kg dose significantly attenuated morphine-induced conditioned place preference in C57BL/6 mice [98, 178]. Although behavioral controls were used in the aforementioned study [159], it is incumbent upon the authors of the present review to note that such a high dose of MPEP may have had off-target activity [179]. Another study reported a similar observation, showing that intracerebroventricular (i.c.v.) MPEP treatment was able to completely abolish morphine induced conditioned place preference in ICR mice, and also noted that PKC $\gamma$  was induced in the limbic forebrain after the conditioning, a phenomenon that was blocked by the administration of MPEP [180]. Studies in rats also show that doses of MPEP that do not impair spontaneous locomotion have no effect on morphine reward [97]. A recent study has shown that MPEP dose-dependently attenuated self-administration of ketamine in rats, while only the highest dose investigated (20mg/kg) was able to impair responding for heroin [181].

### Cannabinoids

An endogenous target for  $\Delta^9$ -tetrahydrocannabinol (THC), the psychoactive cannabinoid found in marijuana, was cloned in 1990 and is now known as the CB<sub>1</sub> receptor [182]. To date there has been relatively little research on group I mGlu receptors with regard to their possible involvement in marijuana use. However, there is substantial evidence pointing towards a significant physiological link between mGlu1/5 and CB<sub>1</sub> receptors, in that mGlu5 receptors activate pre-synaptic populations of CB<sub>1</sub> receptors [183]. Studies in rat brain slices of the corticostriatal synapse and within hippocampus have shown mGlu5-dependent activation of an intracellular signaling pathway involving PLC- $\beta$ , an endpoint of which is synthesis of

the endocannabinoid 2-arachidonoylglycerol (2-AG), which activates CB<sub>1</sub> receptors [184, 185]. Furthermore, activation of post-synaptic mGlu1/5 populations is required for LTD mediated by CB<sub>1</sub> receptors [186]. Finally, cannabinoid-mediated antinociception is dependent on mGlu5, but not on mGlu1 [187]. However, the main thrust of research in this area appears to be directed at the role of the endogenous cannabinoid system in responses to other drugs of abuse. Modulation of this system is involved in cocaine addiction [188], and CB<sub>1</sub>-mediated LTD is abolished by a single *in vivo* exposure to cocaine, a phenomenon that coincides with a decrease in mGlu5 surface expression in the NAc [67].

### INTERACTIONS BETWEEN MGLU1 AND MGLU5 RECEPTORS

There are numerous studies that have shown that when treated together, mGlu1 and mGlu5 seem to have a more significant physiological role than when they are manipulated alone. An elegant example of this is the electrophysiological study conducted by Gubbelini and colleagues in 2003, in which slices from mGlu5-deficient mice were treated with a selective mGlu1 receptor antagonist and slices from mGlu1-deficient mice were treated with an mGlu5 antagonist [189]. The results conclusively showed that corticostriatal LTP was attenuated in the slices deficient in either of the two receptor subtypes, and that application of the complementary antagonist was able to completely abolish LTP, as was co-administration of both antagonists in wild type slices. Combined activity of mGlu1 and mGlu5 is required for the early component of group I mGlu-potentiated LTD [69]. Moreover these two highly related receptors appear to utilise distinct intracellular signalling pathways to achieve the same endpoint, such as activation of ERK [190] and enhancing ionotropic glutamate responses [148]. Upon activation by glutamate, mGlu1-expressing cells display a non-oscillatory intracellular calcium response, while mGlu5 cells display an oscillatory response [191]. This is due to the presence of a threonine residue at position 840 in mGlu5 which creates a consensus PKC binding site that is absent in mGlu1, which contains an aspartate residue at the corresponding position [191]. This may in part explain the necessity for both receptor subtypes to elicit maximal physiological responses in certain situations. For example, antagonism of either the mGlu1 or mGlu5 receptor attenuated morphine tolerance, while co-administration of both receptor antagonists completely blocked tolerance [192]. It has also been shown that administration of the non-selective group I mGlu antagonist S-4-CPG completely abolished amphetamine-induced hyperlocomotion in rats [193], while other studies have shown that blockade of mGlu5 alone only attenuates amphetamine-induced hyperlocomotion [106, 194].

### CONCLUDING COMMENTS

It is interesting to speculate on the possibility of group I mGlu antagonists being used as therapeutic agents in the treatment of drug and / or alcohol addiction. Given the large body of evidence available, it seems that our knowledge is sufficient to begin designing agents for clinical trials. However, as with any pharmacological therapeutic, there must be a close examination of the potential benefits balanced against the potential risks. For example, a candidate molecule with low probability or low severity of adverse drug reactions coupled with a high therapeutic benefit would be well justified for further development. Unfortunately, it is in this balance that mGlu receptor antagonists encounter a stumbling block. The similarities between addiction and learning and memory systems are well documented (eg. [195]), and mGlu5 in particular has repeatedly been shown to be critical in learning and working memory in rodent models [153, 196-199]. However, acamprosate, which is approved by the Federal Drug Administration of the USA for use in treating alcoholism, is believed to elicit physiological effects in part

through negative modulation of mGlu5 receptors. It has been proposed that this modulation is not a full blockade, allowing the drug to attenuate the hyperglutamatergic state associated with alcohol abstinence without impairing learning and memory functions of which mGlu5 is a critical component [140]. It is important to note that only a subpopulation of neurons will be in a hyperglutamatergic state at any given time, and it is possible that acamprosate preferentially targets mGlu5 receptors on these neurons rather than those on neurons that remain in the basal state. Thus, it may be possible to target an mGlu5 antagonist to certain regions of the brain by virtue of the “hyperglutamatergic status” of different projections under specific circumstances (such as withdrawal), producing full blockade in regions involved in driving relapse to drug-seeking, but not in those critical for classical learning and memory.

There is also keen interest in other members of the metabotropic glutamate receptor family with regard to developing therapeutics for drug addiction, particularly group II agonists. Like antagonism of post-synaptic mGlu5 receptors, activation of pre-synaptic mGlu2/3 receptors result in attenuation of excessive glutamate release; thus agonists at these receptors may also be useful therapeutics in treating drug addiction [200]. Indeed, research on mGlu2/3 receptor agonists with regard to drug addiction is a field unto itself, and there are findings showing that reinstatement of both cocaine [201] and heroin [202] seeking can be attenuated by administration of LY379268, an mGlu2/3 receptor agonist.

As mentioned earlier, it appears that manipulating both group I receptor subtypes in tandem appears to have a greater effect than treating each individually. However, the fact that both subtypes are critical for corticostriatal LTP in slices makes the possibility of full group I receptor blockade as a therapeutic option possibly even more remote than blockade of an individual subtype [189]. One possibility for safely utilising mGlu5 modulation with regard to alcohol addiction is based on a recent finding regarding the interaction between mGlu5 and A<sub>2</sub>A receptors [163]. A large reduction in ethanol drinking was observed when the antagonists were co-administered at doses considered subthreshold when treated individually. It also appears to the authors that mGlu1 has been unduly ignored by the research community during the flurry of interest in mGlu5. Understanding how both receptor subtypes are involved in the process of addiction may yet yield important information that may be utilised in designing future therapeutics, which may or may not take advantage of interactions with other systems. Another potential avenue for the ultimate use of group I mGlu receptor compounds clinically could be at low doses in a “poly-pharmacy” approach with current (or yet to be discovered) therapeutics. Finally, there may be a potential for genetic manipulation of aberrant polymorphisms and/or pharmacogenomic profiling of subjects who respond favourably to manipulation of group I mGlu receptors.

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