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# The role of metabotropic glutamate receptors in addiction: Evidence from preclinical models

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ABSTRACT

Addiction is a chronic disorder characterised by repeated bouts of drug taking, abstinence and relapse. The addicted state may be in part due to drug-induced neuroadaptations in the mesocorticolimbic and corticostriatal pathways. Recently focus has been on the role of aberrant glutamate transmission and its contribution to the hierarchical control over these systems. This review will expand our current knowledge of the most recent advances that have been made in preclinical animal models that provide evidence that implicate metabotropic glutamate receptors (mGluRs) in contributing to the neuroadaptations pertinent to addiction, as well as the role of Homer proteins in regulating these responses. The recent discovery of receptor mosaics will be discussed which add an additional dimension to the complexity of understanding the mechanism of glutamate mediated behaviours. Finally this review introduces a new area related to glutamatergic responses, namely microRNAs, that may become pivotal in directing our future understanding of how to best target intervention strategies to prevent addictive behaviours.



## 1. Introduction

### 1.1. Addiction

Drug addiction, relating to both licit and illicit substances, is a serious socio-economic problem affecting an estimated 9.2% of the population directly (Aldworth et al., 2007), with an equivalent impact on the user's family and friends. In Australia alcohol related costs alone, for example, have recently been estimated to total more than $36 billion AUD annually; $24.7 billion relating to tangible costs (expenses, wages) and $11.4 billion in intangible costs (diminished quality of life) (Laslett et al., 2010). This more than triples that of cancer and cardiovascular disease combined (Cancer Council of Australia, 2010; CATI Technical Reference Group, NPH, 2003). Furthermore, it is estimated that drug related issues consume up to 3.5% of the gross domestic product in western countries (Pouletty, 2002), which is equivalent to $485 billion in the USA alone (Agency, 2008). Addiction has been defined as the loss of control over compulsive drug-seeking and taking that continues despite significant negative consequences (Hyman and Malenka, 2001). It has been suggested that in individuals the development of an addicted state is due to neuroadaptive changes in the brain upon repeated exposure to drugs of abuse that become persistent. These changes can lead to altered behaviour and be a driving force to continue drug-seeking (see Kalivas and Volkow, 2005; Feltenstein and See, 2008; Koob and Volkow, 2010). Individual variability in the vulnerability to addiction following drug use is also apparent being influenced by genetic, biological and environmental factors (Piazza et al., 1989; Belin et al., 2011). Addiction is associated with multiple cycles of relapse following attempts to stop, or reduce, drug use (see Koob and Volkow, 2010).

Whilst drugs of abuse have diverse pharmacological profiles they share common acute actions on the mesocorticolimbic dopaminergic pathways. These pathways originate in the ventral tegmental area (VTA) of the midbrain and connect to the limbic system via the nucleus accumbens (NAcc), amygdala, hippocampus and prefrontal cortex acting primarily to modulate behavioural responses related to reward and reinforcement (Le Moal and Simon, 1991). Acute exposure to a drug of abuse increases dopamine release primarily in the NAcc, greater than a natural reward (food or sex), and thus activity in this pathway. However unlike natural rewards, dopamine release may be maintained following drug exposures possibly reinforcing reward learning (Di Chiara, 2002). Whilst dopaminergic processes appear responsible for the acute rewarding affects of drugs of abuse the failure to control drug-seeking behaviours and persistent drug taking is more complex. For example, an enduring imbalance in the glutamatergic regulation of corticostriatal information processing has led to the glutamate hypothesis of addiction (Kalivas, 2009). Acute exposure to psychostimulants normally increases extracellular glutamate levels in the NAcc (McFarland et al., 2003), prefrontal cortex (Reid et al., 1997) and to a lesser degree the VTA (Kalivas and

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Duffy, 1998). This increases the sensitivity of glutamate receptors to subsequent exposures at lower doses (Reid and Berger, 1996). Ultimately resulting in a depression of extracellular glutamate levels over repeated exposures and decreased glutamate driven activity that can persist up to 5 days into extinction (Miguens et al., 2008). Chronic exposure to psychostimulants also results in altered metabotropic glutamate receptor (mGluR) trafficking and expression of both Group I and Group II mGluRs in a subunit and region specific manner (Freeman et al., 2001; Xi et al., 2002b; Mitrano et al., 2008). Following a period of abstinence, re-exposure to the drug directly or a drug associated cue enhances synaptic glutamate release believed to play a role in mediating reinstatement (Kalivas, 2009; Reid and Berger, 1996). These affects may be time dependent as during extinction suppressed basal glutamate levels slowly return to normal becoming less responsive to re-exposure (Miguens et al., 2008). Thus, the fine tuning of signal transmission of dopaminergic projections from the VTA to medium spiny neurons (MSNs) in the NAcc is highly influenced by glutamatergic inputs from the prefrontal cortex, amygdala and other structures. The NAcc serves as a key interface between the limbic (processing of new and learnt information) and motor (task performance) subunits which enables the limbic subunit to modify adaptive outcomes. Impaired glutamate transmission may affect the ability of the limbic pathway to adequately process the adverse consequences associated with continued drug taking leading to maintenance of the motor subunit and drug-seeking behaviours (Kalivas, 2009). Consequently, the modulatory roles of glutamatergic processes have gained increasing interest as an allosteric shift towards augmented glutamatergic function might contribute in the transition from controlled drug use to a compulsive and uncontrolled drug dependent state and the high incidence of relapse.

### 1.2. Glutamate receptors

L-glutamate is one of the major excitatory neurotransmitters in the mammalian central nervous system. Release of glutamate from synaptic vesicles at the presynaptic cleft activates ligand gated ion channels (ionotropic glutamate receptors, iGluRs) including N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic-acid (AMPA) and kainic acid receptors, which are primarily located postsynaptically mediating fast excitatory neurotransmission (Kew and Kemp, 2005). Alternatively, glutamate binds to and activates mGluRs, 7 transmembrane domain G-protein coupled receptors (GPCR, class C) located pre, post, and perisynaptically mediating transmission in a slow modulatory fashion via second messenger signalling pathways (Kew and Kemp, 2005). To date 8 distinct mGluRs have been characterised having overlapping yet distinct neuroanatomical distributions, pharmacological and intracellular properties (see Niswender and Conn, 2010). These receptors can be subdivided into 3 groups (Groups I, II, and III) based on their sequence homology, G-protein coupling and pharmacology. Group I includes mGluRs 1 and 5, Group II includes mGluRs 2 and 3, and Group III includes mGluRs 4, 6, 7 and 8. The widespread distribution of mGluRs throughout the brain, being expressed by both neurons and glia provides an ideal target for modulatory roles over cell excitability and synaptic transmission with regard to addictive behaviours. These receptors also play a key role in memory and learning (Gil-Sanz et al., 2008) and regulate iGluR function (Rosenbrock et al., 2010), synaptic plasticity (Tominaga-Yoshino et al., 2008) and neuronal pathways. However, the activation of different subtypes results in diverse actions across neural systems adding to the complexity of understanding the specific roles of mGluRs in mediating aspects of addiction.

There is some evidence Group III mGluRs, especially mGluR4, may be involved in mediating addictive behaviours (Mao and Wang, 2000; Blednov et al., 2004). For the purpose of this review, we will focus on Group I and II receptors. These receptors (Niswender and Conn, 2010) and their roles in mediating specific behaviours such as drug-seeking and relapse have recently been reviewed (for Group I see Bird and Lawrence, 2009; Olive, 2009; Olive, 2010 and for Group II see Moussawi and Kalivas, 2010). This review will expand on certain themes that have been previously raised, consolidating and highlighting new advances from preclinical models that strengthen the support of a role for mGluRs in mediating key aspects of addictive behaviours. We will present new insights into the roles of both Group I and Group II receptors in addiction with a focus on synaptic plasticity, memory and learning (including extinction), the role of Homer proteins, positive allosteric modulators and higher order receptor mosaics. We will also review novel information on the potential interactions between microRNAs and mGluRs in the mediation of drug-seeking, a new and under explored area of research with regard to glutamatergic involvement.

### 1.3. Group I receptors: mGluR1 and mGluR5

Widespread throughout the central nervous system, Group I receptors are expressed by neurons (mGluR1 and mGluR5) and glia (mGluR5) serving distinctly different roles in these two cell populations (Castillo et al., 2010). In neurons, Group I receptors are predominantly located postsynaptically around the perisynaptic annulus of dendritic spines where their activation leads to depolarization, resulting in increased neuronal activity (Niswender and Conn, 2010). This serves primarily to facilitate glutamatergic transmission and potentiate NMDA receptor currents. Group I mGluRs are coupled to $Gq/G_{II}$ proteins and upon activation initiate the phospholipase C (PLC) pathway and mobilise calcium release from inositol 1,4,5-trisphosphate (IP3) mediated stores, both processes resulting in increased intracellular calcium levels (Conn and Pin, 1997; Ahn et al., 2010). A small number of Group I receptors have also been identified presynaptically (Rodrigues et al., 2005), where they are believed to play a role in modulating glutamate release.

Whilst Group I receptors share many physiological properties, they appear to have region-specific differential sensitivities to drugs of abuse. The expression of mGluR1 is relatively low in nuclei associated with the mesocorticolimbic system such as the dorsal striatum, amygdala, NAcc and prefrontal cortex. Higher expression is seen in the hippocampus, hypothalamus, lateral septum and cerebellum (Lavreysen et al., 2004). As mGluR1s are not heavily expressed in traditional “reward” pathways and there are few selective ligands specific for mGlu1 receptors, investigation into their role in mediating addictive behaviours has been comparatively limited. Indeed inhibition of mGluR1 with the antagonist EMQMCM (JNJ16567083, (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate) attenuates behavioural sensitization to cocaine, the same affect not being observed if mGluR5s are targeted (Dravolina et al., 2006). The same group has also reported that EMQMCM inhibits cue and priming-induced reinstatement for nicotine (Dravolina et al., 2007) and improves working memory, reducing impulsiveness (Sukhotina et al., 2008). However, mGluR1 has received relatively little attention of late with the few exceptions highlighted below in this review. In contrast to mGluR1, mGluR5s are highly concentrated in nuclei associated with reward pathways such as the forebrain and limbic structures, dorsal striatum, NAcc, lateral septum, hippocampus, and cerebral cortex (Shigemoto et al., 1993; Romano et al., 1995).

For nearly a decade mGluR5s have been implicated as key players in mediating the behavioural responses to drugs of abuse, especially cocaine. Metabotropic Glu5 receptor knockout mice reportedly do not self-administer cocaine nor do they apparently display the typical hyperlocomotive responses to cocaine even though cocaine-induced dopamine levels in the NAcc are similar to wild type animals (Chiamulera et al., 2001). More recent data suggest that mGluR5 knockout mice do sensitise to cocaine (Bird et al., 2010). Cocaine-self administration is also reduced in wild type animals injected with the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) adding support to the contribution of mGluR5s in regulating cocaine

induced behaviours (Chiamulera et al., 2001). Since the initial findings by Chiamulera et al. (2001) there has been considerable evidence that mGluR5s are heavily involved in mediating responses to cocaine including self-administration, reward learning (Novak et al., 2010), both prime- and cue-induced reinstatement (Kumaresan et al., 2009) and a particular role in extinction (Gass and Olive, 2009; Knackstedt et al. 2010). It has been suggested that both Group I and Group II receptors play roles in the regulation of the dopamine responses following exposure to methamphetamine (Shimazoe et al., 2002). More recent data have shown that MPEP is able to reverse the methamphetamine induced dopamine efflux in striatal tissues (Golembiowska et al., 2003). The mGluR5 antagonist [(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) can reduce self-administration of methamphetamine (Osborne and Olive, 2008; Gass et al., 2009) and prevent both drug- and cue-induced reinstatement of methamphetamine-seeking behaviours (Gass et al., 2009). Antagonism of mGluR5, but neither mGluR1 antagonism nor, mGluR2/3 agonisim, is sufficient to inhibit methamphetamine induced neurotoxicity (Battaglia et al., 2002). In addition, exposure to methamphetamine selectively increases Homer1a levels in the striatum and NAcc, whilst Homer1b or 1c levels are not affected, though this was following a high dose (40 mg/kg, i.p.) (Hashimoto et al., 2007). Together these data suggest that the actions of methamphetamine are primarily via Homer1a/mGluR5 mediated mechanisms (see below), yet further clarification of these observations is needed.

There is also mounting evidence that mGluR5s may play a considerable role in the regulation of the addictive properties of alcohol. Using genotype profiling human genetic studies have identified that individuals with genetic variations in mGluR5, along with the NMDA NR2A receptor subunit, have the highest risk of developing alcohol dependence when compared to control patients based on diagnostic interview (Schumann et al., 2008). This association is supported by data from animal studies that have shown mGluR5s are involved in regulating the onset (Hodge et al., 2006) and motivation to self-administer alcohol (Cowen et al., 2005; Cowen et al., 2007; Besheer et al., 2008b) as well as binge alcohol consumption (Tanchuck et al., 2011). Metabotropic GluR5-deficient mice voluntarily consume less ethanol than wild type litter mates (Bird et al., 2008) and are more sensitive to the hypnotic effects of ethanol (Bird et al., 2008; Downing et al., 2010). It is of interest that these animals display a conditioned place preference (CPP) to low doses of ethanol (1 g/kg) insufficient to produce a CPP in wild type littermates. This suggests an increased sensitivity to ethanol's centrally mediated rewarding affects in knock-out animals, as there was no difference between genotypes in the rate at which ethanol was metabolised by the liver (Bird et al., 2008). In alcohol-preferring rats MPEP injected into the NAcc reduces ethanol self administration. This affect is not seen if MPEP was infused into the dorsomedial caudate or medial prefrontal cortex (Besheer et al., 2010). Furthermore, this response appears specific to mGluR5s as infusion of the mGluR2/3 agonist LY379268 produces non-specific affects on responding (Besheer et al., 2010) even though both ligands, via different mechanisms, act to reduce glutamate-mediated excitation.

Inhibition of mGluR5 is also sufficient to attenuate nicotine self-administration (Paterson et al., 2003; Paterson and Markou, 2005), the ability of nicotine to enhance responding when paired with a weak reinforcer (Tronci et al., 2010) and impair nicotine induced CPP (Yararbas et al., 2010). It is of interest that the effects of nicotine, with regard to its reinforcing properties in a CPP paradigm, are only observed in male rats (Yararbas et al., 2010). A similar result has been reported for lysergic acid diethylamide (LSD) induced CPP (Meehan and Schechter, 1998). As such MPEP treatment would be ineffective in female rats from these groups. In contrast female rats are more sensitive to the conditioning effects of cocaine requiring fewer and lower doses to induce a CPP (Russo et al., 2003b), with female rats displaying a more robust sensitization to cocaine than males (Cailhol and Mormede, 1999). Furthermore, female mice appear more susceptible to increased ethanol-self administration over a limited access (2 h) paradigm and binge drinking behaviours (Strong et al., 2010). These sex differences have been suggested to be dependent on the influence of gonadal hormones on drug reward (Cailhol and Mormede, 2001; Russo et al., 2003a). Intact female rats display a stronger reinstatement to cannabinoid-seeking after exposure to a drug prime or cue when compared to both male and ovariectomized females, however latency to first response is not different between intact and ovariectomized females (Fattore et al., 2010). Exposure to gonadal hormones is able to regulate the expression of Group I mGluRs (Hilton et al., 2006) and stimulates signalling of both Group I and Group II receptors (Boulware et al., 2005). This occurs via direct coupling between oestrogen and mGluR receptors in a region and subunit specific manner (Boulware et al., 2005; Grove-Strawser et al., 2010). Together these data suggest that sex and oestrogen cycle may influence drug-seeking behaviours and investigation into sex differences needs to be a future consideration when trying to understand the mechanisms mediating addiction and affective treatment strategies.

### *1.4. Positive allosteric modulators and Group I receptors*

Positive allosteric modulators (PAMs) provide an alternative to direct receptor activation by targeting regions of the receptor not occupied by ligands and potentiating responses of sub-threshold doses of other compounds (inducing a leftward shift in a glutamate response curve). They do not affect binding to the orthosteric site and display little activity alone (see Conn et al., 2009). Using midbrain slice cultures it has been demonstrated that PAMs can selectively potentiate subunit specific-mediated responses (i.e. mGluR5) without affecting responses mediated by close relatives (i.e. mGluR1 or mGluR2) (Chen et al., 2007). However, the precise site of action and effectiveness of PAMs is still being debated. More recent studies have shown that the PAM 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB) forms a competitive interaction with the binding site for the negative allosteric modulator MPEP sharing a partly overlapping binding site (Chen et al., 2007). At high concentrations CDPPB can also directly activate mGluR5s in the absence of glutamate (Kinney et al., 2005).

Studies regarding PAMs for mGluR1 have so far been based on the establishment of pharmacologically effective molecules (Knoflach et al., 2001; Chen et al., 2008b). In contrast, PAMs specific for mGluR5s reportedly promote NMDA receptor function (Rosenbrock et al., 2010; Vardigan et al., 2010), are able to reverse amphetamine induced hyperlocomotion (Rodriguez et al., 2010) and mediate calcium signalling (Bradley et al., 2009). Treatment with CDPPB facilitates the extinction of a cocaine induced CPP (Gass and Olive, 2009) suggesting that PAMs may be useful in enhancing extinction, especially with regard to contextual memory. The same effect is not observed with co-administration of MTEP or MK-801 (Gass and Olive, 2009). It is possible that the affect on extinction may be linked to the ability of PAMs to alter mGluR5 dependent long-term potentiation (LTP) and long-term depression (LTD) (see below), at least in CA1 Shaffer collaterals, improving cognitive function (Ayala et al., 2009). CDPPB also enhances the firing rate and burst activity in medial prefrontal cortical neurons (Lecourtier et al., 2007). Unlike the rapid desensitisation that can occur with direct receptor ligands, the effects of CDPPB on neuronal activity are prolonged, again highlighting the potential benefits of PAMs as treatment therapies (see Homayoun and Moghaddam, 2010 for discussion). Further investigation into their application to Group I receptors is needed as Moussawi et al. (2009) have shown that CDPPB diminishes the beneficial effects of *N*-acetylcysteine on cocaine-seeking, actually acting to promote relapse (Moussawi et al., 2009).

The use of PAMS as therapeutic agents, as opposed to antagonists or agonists, is growing in momentum. This is due to the fact that the actions of ligands appear dependent on the pharmacological class of

drug being abused; they often bind to greater than one receptor subtype and may produce undesirable behavioural affects especially in light of the discovery of higher order oligomers (see below). For example, whilst the negative allosteric modulator MPEP may be beneficial in reducing self-administration of cocaine (Paterson and Markou, 2005), nicotine (Paterson and Markou, 2005; Paterson et al., 2003) and ketamine (van der Kam et al., 2007), high doses are required to produce only a modest reduction (20%) in the self-administration of heroin (van der Kam et al., 2007). It has also been shown that MPEP potentiates, not attenuates the rewarding affects of heroin in inducing a CPP at a moderate dose (10 mg/kg i.p) not sufficient to alter locomotor activity (van der Kam et al., 2009a). MPEP itself has weak positive reinforcing and rewarding effects on self-administration. Self-administration is maintained following substitution of MPEP in rats that have been trained to administer ketamine or heroin, with drug naïve rats self-administering MPEP for over 7 sessions (van der Kam et al., 2009b). Indeed pre-treatment with MPEP in association with nicotine, cocaine, buspirone or clonidine can potentiate the acquisition of drug-induced reward (Rutten et al., 2011) together suggesting that the reduction in self-administration observed following MPEP may be due to potentiation of the rewarding affects of drugs of abuse (van der Kam et al., 2009b). MPEP may also significantly affect the activity of both NMDA (O'Leary et al., 2000) and mGluR4 (Mathiesen et al., 2003) receptors. Consequently combination therapies may be required to successfully target the cessation of drug taking with PAMs. Thus, PAMs could possibly combat the initial phases of drug-seeking during abstinence acting to enhance extinction whilst negative allosteric modulators may be of utility to counteract drug craving subsequent to extinction.

### 1.5. Group II receptors: mGluR2 and mGluR3

Recently Modafinil, a wake-promoting agent has been suggested as a potential treatment option for drug dependence as it was able to block primed reinstatement of an extinguished morphine CPP (Tahsili-Fahadan et al., 2010). This inhibition appears dependent on stimulation of mGluR2/3s. The mGluR2/3 agonist LY379268 has been shown in rats to be more effective than MTEP in reducing ethanol-seeking (Sidhpura et al., 2010), blocks recovery of extinguished ethanol-seeking induced by drug associated cues (Zhao et al., 2006) and is neuroprotective following binge (4 day) alcohol exposure associated with prevention of deficits in spatial reversal learning (Cippitelli et al., 2010). Together these observations have lead to a growing interest in understanding the roles of mGluR2/3s as a therapeutic target for drug addiction as agonists exert inhibitory tone on the receptors compensating for glutamate imbalances following exposure to drugs of abuse (Kalivas, 2009). Metabotropic Glu2/3 receptors are predominantly located presynaptically on glutamatergic neurons where they act as inhibitory autoreceptors to suppress neuronal activity via differing mechanisms including direct vesicular release, glutamate release (Xi et al., 2002a) or synaptic availability (Kalivas, 2009). They are also found presynaptically at inhibitory gamma-aminobutyric acid (GABA)ergic synapses, amongst others (see Niswender and Conn, 2010). Smaller numbers are found postsynaptically where upon activation they can induce hyperpolarization (Muly et al., 2007). Metabotropic GluR2/3s couple to $G_i/G_o$ proteins to decrease cyclic adenosine monophosphate (cAMP) levels via inhibition of adenylate cyclase and directly regulate ion channels and other downstream signalling pathways (see Niswender and Conn, 2010). They are also found on astrocytes (primarily mGluR3), their function there is currently unknown. The distribution of mGlu2/3 receptors in the brain is similar to that of mGluR5, but are overall less abundant, with expression being greatest in the hippocampus (though low in CA1) (Blumcke et al., 1996), dorsal striatum, NAcc, amygdala, cerebral cortex (Neki et al., 1996) and cerebellum (Ohishi et al., 1998). To date mGluR2/3s are believed to play a role in the regulation of reward processing and drug-seeking with reduced function after prolonged drug exposure (see Moussawi and Kalivas, 2010 for review).

Development of selective ligands to differentiate the specific functions of mGuR2 and mGluR3 has been difficult. In mice, deletion of either mGluR2 or mGluR3 would suggest that mGlu2 receptors may play a greater role in mediating addictive behaviours (Morishima et al., 2005) where as mGlu3 receptors are involved more heavily in astrocytic mediated neuroprotection (Corti et al., 2007). For example, the deletion of mGluR2 increases the hyperlocomotive responsiveness to acute cocaine and increases CPP following repeated administration even though animals display the expected increase in NAcc dopamine levels normally observed following cocaine exposure (Morishima et al., 2005). The authors argue that the resultant effects are most likely due to the marked differences in glutamate response in these animals. In support, systemic injection of the mGlu2/3 receptor agonist LY379268 to rats 30 min prior to toluene (600 mg/kg, i.p), the active component in products used as inhalants, attenuates its hyperlocomotor affects (Riegel et al., 2003). Whilst this study used 6-hydroxydopamine lesions to illustrate that elevated dopamine levels in the NAcc are likely responsible for toluene's hyperlocomotive affects, this study also illustrates that mGluR2/3 receptors may subsequently be recruited to regulate behaviours following toluene exposure (Riegel et al., 2003). It has more recently been found that the actions of mGluR2/3 appear dependent on their ability to directly influence dopaminergic transmission. Stimulation of mGluR2/3s with the agonist LY354740 is sufficient to inhibit amphetamine induced hyperlocomotion in rats which correlates with an attenuated release of dopamine in the NAcc and dorsal striatum (Pehrson and Moghaddam, 2010). A similar affect on behaviour and neurotransmitter release has been reported for the agonist LY379268 in response to cocaine (Bauzo et al., 2009). It is believed that the normal increase in extracellular dopamine levels following exposure to amphetamine occurs due to inhibition of the vesicular transport and reversal of the dopamine transporter (see Sulzer et al., 2005 for review). Interestingly, in the study by Pehrson and Moghaddam (2010) the effects on dopamine following LY354740 are specific to exposure to amphetamine, as LY354740 is not sufficient to inhibit dopamine release nor behaviour following electrical stimulation or introduction of the dopamine precursor L-dopa (Pehrson and Moghaddam, 2010). Activation of mGluR2/3 with LY379268 (3 or 10 mg/kg) is also insufficient to effect the rate of dopamine synthesis, at least in reserpine-treated rats (Fell et al., 2009). The authors concluded that activation of mGluR2/3s by amphetamine attenuates dopamine release through impulse flow independent mechanisms such as reduced activation of cortical feedback loops and is not seemingly based on activity dependent vesicular release, uptake or synthesis (Pehrson and Moghaddam, 2010).

### 1.6. Positive allosteric modulators and Group II receptors

In rats, systemic administration of the PAM N-acetylated-alpha-linked-acidic dipeptidase inhibitor 2-(phosphonomethyl)pentane-dioic acid (2-PMPA) attenuates intravenous cocaine self-administration and cocaine-induced reinstatement presumably by increasing the levels of N-acetyl-aspartylglutamate (NAAG), an endogenous mGluR2/3 ligand (Xi et al., 2010). The affect of cocaine-induced reinstatement appears site specific as microinjections of 2-PMPA or NAAG are only affective when injected into the NAcc, but not the dorsal striatum. The effect can be blocked by intra-NAcc injections of the mGluR2/3 antagonist LY341495, which has resultant effects on both dopamine and glutamate levels (Xi et al., 2010). In contrast, in the medial prefrontal cortex the mGluR2 PAM LY487379 enhances extracellular levels of both norepinephrine and serotonin with minimal affects on dopamine and glutamate in this region (Nikiforuk et al., 2010). The mGluR2 PAM potassium 3′-([(2-cyclopentyl-6-7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)biphenyl

l-4-carboxylate (BINA) is sufficient to block phencyclidine-induced hyperlocomotor activity (Hackler et al., 2010). In addition BINA decreases cocaine self-administration and cue-induced reinstatement in rats given both short (1 h) and long (6 h) access to cocaine without affecting food responding. In contrast, to the agonist LY379268 affecting both cocaine and food response (Jin et al., 2010). The success of PAMs may be due in part that they are able to facilitate the activation of receptors without themselves causing over stimulation (Rosenbrock et al., 2010), which may occur following exposure to agonists, providing an interesting avenue for further investigation.

### 1.7. The role of mGluRs in synaptic plasticity

Synaptic plasticity is critical in reward based learning. Upon repeated exposure to psychostimulants structural alterations, including synaptic plasticity, are thought to become impermeable to change and have been suggested to be part of the biological basis of the transition to, and enduring nature of, an addicted state (for reviews see Malenka and Bear, 2004; Kauer and Malenka, 2007). Dendritic spine density and morphology greatly influence plasticity and can be modified in response to the neuronal activity stimulated following exposure to drugs of abuse. Verpelli et al. (2010) have shown that the transition of neuronal activity to local protein synthesis appears regulated by activation of mGluR5. In rat hippocampal neurons application of MPEP reduces bicuculline induced brain-derived neurotrophic factor (BDNF) synthesis (but not mRNA expression) via modulating phosphorylation of the eukaryotic elongation factor 2 (eFF2), which regulates protein translation and elongation (Verpelli et al., 2010). The activity-dependent synthesis of proteins, including BDNF, mediates structural changes to dendritic spines (Tanaka et al., 2008), as well as modulating LTP (Ji et al., 2010; Ninan et al., 2009) and LTD (Egashira et al., 2010). Long-term potentiation and LTD are two hallmarks of long-lasting synaptic plasticity. Long-term potentiation permits strengthening of synapses whilst LTD is associated with weakening of synapses, and together their combined actions permit refinement and consolidation of adaptive changes to neuronal circuits following exposure to drugs of abuse (Malenka and Bear, 2004; Kauer and Malenka, 2007). Furthermore, it appears that glutamate is highly involved in the regulation of these enduring alterations. For example, Tominaga-Yoshino et al. (2008) have shown that repeated, but not single, inductions of LTP in cultured rat hippocampal slices via exposure to glutamate leads to synaptic enhancement (Tominaga-Yoshino et al., 2008) with both mGluR1s and mGluR5s contributing to this induction (Schotanus and Chergui, 2008). This is accompanied by long-lasting changes in the expression of synapse-related genes which occurs in two phases, one between 24 and 96 h and one 6–12 days after the last exposure (Kawaai et al., 2010). In comparison, repeated mGluR stimulated LTD leads to the elimination of synapses (Shinoda et al., 2005; Shinoda et al., 2010). This process requires rapid novel protein synthesis (within 6 h) (Egashira et al., 2010) and can persist for at least two weeks after the last induction (Shinoda et al., 2010).

The induction of LTP requires amplification of action potential evoked calcium signalling by preceding mGluR activation and the generation of IP3 (Cui et al., 2007; Harnett et al., 2009). IP3 controls the activity of the IP3 receptor located on the endoplasmic reticulum and ultimately the release of calcium from IP3 linked intracellular stores (Berridge, 2009). Repeated, but not single, exposure to amphetamine for 3–7 days increases Group I mGluR-dependent action potential-evoked calcium signals in VTA, but not substantia nigra, dopaminergic neurons. This leads to the induction of Group I mGluR mediated NMDAR-LTP (Ahn et al., 2010). The degree of this response correlates to the magnitude of amphetamine induced CPP. This study also showed that following exposure to amphetamine, the increased activity of Group I mGluRs is regulated by protein kinase A (PKA)-induced sensitization of IP3 with facilitation of calcium signalling lasting for up to 10 days after withdrawal (Ahn et al., 2010). As a secondary messenger system increases in intracellular calcium levels are involved in the regulation of enzymatic activity (Bush et al., 1989), gene expression (Hardingham et al., 1997) and altered neurotransmitter release (Nizami et al., 2010). Elevated intracellular calcium levels can also differentially regulate both the magnitude and direction (either potentiation or depression) of synaptic transmission. This process is controlled by activation of mGluR signalling pathways (Nevian and Sakmann, 2006). As such altered calcium signalling, especially in the prefrontal cortex and NAcc during withdrawal, is likely to have enduring effects on the cellular mechanisms mediating behaviour, possibly contributing to relapse (Hu, 2007). Along with long-lasting synaptic plasticity, activity-dependent short term plasticity which lasts only minutes is important for the modulation of synaptic strength during information processing. Short term plasticity can be heterosynaptically mediated via postsynaptic calcium and Homer-mediated mechanisms and is facilitated by injection of IP3, acting to amplify synaptic signals on a common target (Reissner et al., 2010). With regard to drugs of abuse ethanol exposure in cultured rat Purkinjie cells is sufficient to induce changes to calcium signalling. High doses (33–66 mM) of ethanol depress calcium signalling linked to iGluRs whilst low doses (10 mM) enhance calcium signalling linked to mGluR activation, presumably mGluR1, the primary mGlu receptor expressed by Purkinjie cells (Gruol et al., 1997). This suggests that low doses of ethanol are sufficient to stimulate calcium signalling pathways and have the potential to alter excitatory transmission via mechanisms normally restricted to glutamate signalling (Gruol et al., 1997).

Unlike LTP, more recent evidence suggests that the maintenance of an addicted state may be in part dependent on the ability to induce and enduringly impair LTD. Following operant cocaine self-administration in rats there is a deficit in LTD in the NAcc core and shell during the initial stages of abstinence. Suppression of LTD is only maintained in the NAcc core as abstinence proceeds (Martin et al., 2006). Indeed Group I mGluR-induced LTD normally dissipates within 24 h, but repeated induction leads to a persistent reduction in LTD lasting weeks (Shinoda et al., 2005). Kasanetz et al. (2010) have recently shown that in the initial phase of learning in a cocaine self-administration paradigm LTD is not impaired, however once learning has been consolidated LTD is suppressed in all animals. In animals that developed characteristic addictive behaviours there is an unrecoverable suppression of LTD at corticostriatal synapses in the NAcc. In "non" addicted animals LTD progressively recovers even though animals maintain a controlled drug intake (Kasanetz et al., 2010). In this study no difference was found for mGluR2/3 mediated LTD, though other mGluRs were not tested and can therefore not be ruled out as potential contributors to these responses. Indeed intracerebroventricular injection of MPEP does not affect basal synaptic transmission, but prevents stimulation of LTD (Popkirov and Manahan-Vaughan, 2010) whilst mGluR5s in the NAcc appear involved in the suppression of LTD following acute exposure to cocaine (Fourgeaud et al., 2004). In contrast, self-administration of cocaine, food or a natural reward all potentiate VTA neurons. This potentiation is only maintained in cocaine-exposed rats (Chen et al., 2008a). In cocaine self-administering rats this was maintained for up to 3 months during abstinence, an effect that was not dependent on the presence of cocaine itself. Passive exposure, when cocaine was not paired with cues, did not yield the same affect. This suggests that the potentiation of glutamate function on VTA dopaminergic neurons depends on not just the pharmacological properties of the drug, but is an associative process (Chen et al., 2008a).

Withdrawal from cocaine self-administration impairs the ability of prefrontal cortical stimulation to produce both LTP and LTD in the NAcc. This can be restored by application of the procysteine drug *N*-acetylcysteine, which increases gluthathione synthesis thus activating the cystine–glutamate exchanger (Moussawi et al., 2009). *N*-acetylcysteine is also sufficient to inhibit drug-seeking through mGluR2/3 mediated mechanisms supporting the role of the cystine–glutamate

exchanger in regulating glutamate levels (Moran et al., 2005; Kalivas, 2009). Interestingly Moussawi and colleagues have shown that mGluR2/3 antagonism prevents *N*-acetylcysteine's promotion of LTP specifically whilst *N*-acetylcysteine's affects on LTD were mediated by mGlu5 receptors (Moussawi et al., 2009). This is in contrast to the observation that mGluR2 knockout mice have normal hippocampal LTP, but impaired LTD (Yokoi et al., 1996). Furthermore blocking LTD at glutamatergic synapses in the NAcc is sufficient to prevent the expression of amphetamine-induced behavioural sensitization (Brebner et al., 2005). In contrast behavioural sensitization does not appear to be linked to the ability to induce LTP of VTA cells. In wild type mice following a single exposure to cocaine there is an increase in AMPA/NMDA post-synaptic currents at excitatory synapses onto dopamine neurons in the VTA (Bird et al., 2010). This increase is not observed in mGluR5-deficent mice following cocaine, even though mGluR5 deficient mice still express sensitization to repeated cocaine (Bird et al., 2010). Others have suggested that synaptic plasticity of corticostriatal glutamatergic inputs onto neurons expressing D1 dopamine receptors play an integral role in behavioural sensitization to cocaine (Heusner and Palmiter, 2005). In animals that have undergone sensitization to cocaine there is a reduction in the magnitude of LTD at excitatory synapses made by prefrontal cortical afferents onto MSNs in the NAcc shell (Thomas et al., 2001). These observations support dissociation between drug-induced LTP-like plasticity and behavioural sensitization and that mGlu5 receptors play a key role in the fine tuning of synaptic efficacy on VTA cells, at least for LTP. Though the precise mechanisms mediating behavioural sensitization need further clarification.

### *1.8. The role of Homer proteins in regulating glutamate transmission*

The localization and clustering of mGluRs to the cell surface are critical in mediating synaptic plasticity. Homer is a prominent synaptic scaffolding protein of Group I receptors that anchors receptors to the cell membrane coupling these receptors, particularly mGluR5, to NMDA and IP3 receptors (Tu et al., 1999). In response to neuronal activation, the intracellular protein is able to mediate the function of mGluRs via regulating glutamate transmission, receptor trafficking and intracellular signalling, especially calcium (primarily via IP3) (Tu et al., 1999; Sala et al., 2005; Kammermeier, 2006, 2008). Homer proteins also regulate synaptic plasticity including the size and density of dendritic spines (Sala et al., 2003), being induced by BDNF as a result of synaptic activity (Roloff et al., 2010). Either exposure to (Ben-Shahar et al., 2009), or withdrawal from (Ary and Szumlinski, 2007), cocaine is sufficient to alter Homer expression in a regionally dependent manner corresponding to altered Group I mGluR expression in the same brain regions. For example, in both rats and mice withdrawal from cocaine down-regulates Homer1b/c and Homer2a/b in the NAcc, accompanied by a decrease in mGluR1α expression (Ary and Szumlinski, 2007). In contrast, Homer1b/c, Homer2a/b and mGluR1α are all increased in the hippocampus, whilst only Homer2a/b and mGluR1α are unregulated in the prefrontal cortex with no affect on Homer1b/c in this region (Ary and Szumlinski, 2007). Due to their prominent roles in regulating mGluR expression, and glutamate transmission, Homer proteins have been hypothesised to play a key role in the mediation of the behavioural responses to drugs of abuse. Both Homer1 (Szumlinski et al., 2004) or Homer2 (Kalivas et al., 2004) gene deletion enhances CPP and locomotor sensitization following cocaine exposure in mice. Homer2 deletion also reduces basal extracellular glutamate levels in the NAcc with altered glutamate responding in response to cocaine, however the expected increase in extracellular dopamine is not affected in these animals (Kalivas et al., 2004). In contrast to cocaine, Homer2 knockout mice do not develop a CPP or behavioural sensitization to repeated ethanol exposure (Szumlinski et al., 2005). However, over-expression of Homer2 enhances the response to ethanol (Szumlinski et al., 2008). Chronic ethanol exposure results in increased expression of both mGlu1 receptors and Homer2 which remains elevated for up to 2 weeks after cessation of 3 months ethanol consumption (Szumlinski et al., 2008). Similar enduring changes to both mGluR1 and 5 and Homer2a/b are observed in both the NAcc and the amygdala in more chronically exposed (6 months) rats (Obara et al., 2009). This chronic exposure to ethanol produced long-lasting elevations in the efficiency of postsynaptic glutamate signalling possibly driven by Homer's regulation of mGluR expression. The nature of these responses appears complex. For example, in the study by Obara et al. (2009) alterations to Homer2a/b and mGluR1 and mGluR5 were observed in the NAcc core, involved in associative learning, but not the NAcc shell. In this region these receptors are involved in reinforcing properties of drugs of abuse, with differing responses dependent on whether animals have been permitted continual or intermittent access to ethanol and time points at which the brain was assessed during withdrawal (Obara et al., 2009).

The significance of Homer/mGluR interactions on ethanol consumption cannot be ignored. Intra-NAcc infusions of MPEP are sufficient to attenuate binge alcohol intake in the same manner as virus mediated knock-down of accumbal Homer2b expression. Stimulation of the intracellular signalling cascade phosphatidylinositol 3-kinase (PI3K) (Cozzoli et al., 2009) plays a key role in this response. However, the roles of Homer in mediating the neuroadaptive responses to amphetamine are still being debated. One hour following a single dose of behaviourally active amphetamine (5 mg/kg, i.p) mGluR5 protein levels are decreased in rat striatal synaptosomal plasma membranes, but increased in the medial prefrontal cortex (Shaffer et al., 2010). The mGluR5 levels returning to baseline by 5 h post-exposure corresponding to the behavioural activity induced by amphetamine (Shaffer et al., 2010). These responses are not associated with changes in mGluR1 expression or differences in Homer1b/c expression. The authors suggest that Homer independent mechanisms are likely to underlie the actions of acute amphetamine exposure on mGluR5 expression; however, Homer2 expression was not assessed in this study. The authors also report observations of long-lasting loss of mGluR5 expression in striatal neurons following chronic exposure to amphetamine for 7 days (Shaffer et al., 2010). Similar effects are maintained after 3 weeks of withdrawal from cocaine (Swanson et al., 2001) leading to reduced Homer1b/c proteins in the NAcc in this study (Swanson et al., 2001). Whilst Homer mediated molecular adaptations may play a key role in persistent drug-seeking behaviours, it appears that exposure patterns, duration and withdrawal periods play a critical role in influencing the nature of these Homer/mGluR mediated interactions.

### *1.9. The role of mGluRs in memory and learning*

The transition to an addicted state following exposure to a drug of abuse likely includes a component of associative learning, that is an environmental stimulus is paired with a reward experience acquiring both predictive (availability/location) and incentive (acquisition and conditioned reinforcement) properties (Grossberg et al., 1987; Di Chiara et al., 1999). It is believed that mGluR5s have a dissociative role in mediating predictive compared to incentive learning. Exposure to MTEP prior to Pavlovian conditioning does not affect the motivation of mice to obtain food or discriminate between food-paired stimuli, however mGluR5 signalling did have a critical role in the acquisition of incentive learning (O'Connor et al., 2010). The authors hypothesise that these mGluR5 mediated affects are likely due to induced changes in AMPA receptor expression and that during drug administration these changes may be required for the incentive value of drug-paired cues (O'Connor et al., 2010). This would support drug-seeking and relapse whilst impairing the ability to learn new behaviours other than drug-seeking. Striatal MSNs are the driving force integrating mesostriatal dopaminergic signals and glutamatergic inputs from

cortical and limbic regions. Within the striatum there are two classes of MSN. Those that express dopamine D1 receptors form part of the direct pathway and upon activation result in neuronal excitation. Those expressing dopamine D2 receptors form part of the indirect pathway and upon activation result in neuronal inhibition (Gerfen et al., 1990; Gerfen, 1992). The modulation of dopamine over the direct and indirect pathways determines which signals are reinforced and which are suppressed, differentially contributing to pathological behaviours (Bateup et al., 2010). Novak et al. (2010) took the above observation one step further by demonstrating, using a selective knock-down mouse model, that glutamate signalling through mGluR5s located specifically on striatal MSNs expressing D1-receptors is necessary for the incentive learning processes, at least for cue-induced reinstatement of cocaine-seeking (Novak et al., 2010).

Besheer et al. (2009) have shown that mGluR5s in the NAcc are also involved in regulating the interoceptive affects of alcohol (Besheer et al., 2009), with little contribution from mGluR1s or mGluR2/3 in this role (Besheer et al., 2008a; Besheer et al., 2009). Sidhpura et al. (2010) suggest that mGluR2/3 may play a more important role once adaptive processes have occurred. This group demonstrate that both LY379268 (mGluR2/3 agonist) and MTEP (mGluR5 antagonist) dose-dependently reduced ethanol self-administration and stress-induced reinstatement with LY379268 being more effective in ethanol dependent compared to non-dependent animals (Sidhpura et al., 2010). Rats with longer access to cocaine (6 h daily sessions compared to 1 h daily sessions over 22 sessions) show higher break-points on a progressive-ratio schedule of reinforcement (Hao et al., 2010). In long access rats, the ability of LY379268 to reduce progressive ratio responding is increased whereas the effect of MTEP is only affective in short-access groups (Hao et al., 2010). This corresponds to differing profiles of the mGluR subunits with an increase in functional activity of mGluR2/3s and a decrease in mGluR5s in the long access group. This suggests that dysregulation of both these receptors may play a role in the neuroplasticity important in the transition to dependence (Hao et al., 2010).

As dependence is likely due, in part, to the neuroadaptations that occur following continued drug taking there is only limited success in maintaining abstinence if drug availability is suddenly withdrawn. Considering inhibiting relapse to drug-seeking may be dependent on learning new tasks and consolidation of memories that override the initiation of drug-seeking upon presentation of drug-related cues. There is growing evidence that extinction, which promotes involvement of the prefrontal cortex and NAcc, decreases the adaptive value of drug-seeking (see Kalivas, 2009). Reducing mGlu5 receptor function has been shown to reduce cocaine self-administration (Chiamulera et al., 2001) suggesting a site to target for intervention strategies to prevent drug-seeking. Following 14 days cocaine self-administration extinction training, as opposed to straight withdrawal, leads to a reduction in mGluR5 and Homer1b/c expression in the NAcc (Ghasemzadeh et al., 2009). This reduction is specific to the NAcc shell as the same response is not observed in the NAcc core or dorsal lateral striatum (Ghasemzadeh et al., 2009). These results suggest that extinction training is needed to alter the molecular mechanisms leading to reduced mGluR5 signalling required for sustained abstinence. In support of this hypothesis, contrary to the observations by Ghasemzadeh et al. (2009), more recent evidence has shown that following 3 weeks withdrawal without extinction in rats (following 12 days of constant cocaine self-administration) there is no change in postsynaptic density (PSD) proteins in the NAcc (Knackstedt et al., 2010). However following extinction training, proteins that modulate the expression and clustering of glutamate in the PSD including PSD-95, Homer1b/c and Narp are all elevated in the NAcc core but not the shell. This corresponds to a reduction in mGluR5 in the NAcc core in these animals with no associated change in mGluR1 (Knackstedt et al., 2010). The authors go on to show that whilst stimulation of the prefrontal cortex elicits reduced LTP in the NAcc core of both groups (extinction and withdrawal), only those animals that have been extinguished have blunted LTD. This indicates a clear difference in responses based on whether animals were withdrawn or extinguished during abstinence (Knackstedt et al., 2010). The author's hypothesise that elevated Homer1b/c in the NAcc core may sequester mGluR5 away from the membrane. The reduced expression being sufficient to prevent LTD and thus inhibit cocaine-seeking in rats that have been extinguished. Consequently extinction training is needed to bring the NAcc core into the circuitry involved in preventing abstinent relapse (Knackstedt et al., 2010). This is supported by evidence that when Homer1c is over-expressed in the NAcc core of cocaine-naïve rats LTD is inhibited and similarly over-expression reduces cue-induced reinstatement of cocaine (Knackstedt et al., 2010). In contrast, extinction training does not appear to have the same effect on enhanced synaptic function (LTP). Potentiation at excitatory synapses onto VTA cells persists after 3 weeks of extinction training following self-administration of cocaine potentially driving drug-seeking behaviours (Chen et al., 2008a). This supports the hypothesis that old behaviours remain intake and are not simply "unlearned", and that new contextual behaviours need to be acquired in order to maintain abstinence (Bouton, 2004). Metabotropic GluR5s also appear more important in consolidation of extinction processes rather than their initial acquisition, at least with regard to fear conditioning (Fontanez-Nuin et al., 2011) and extinction of a cocaine induced CPP (Gass and Olive, 2009). More information regarding the precise nature of neural mechanisms mediating differing responses following withdrawal or extinction is needed.

If addiction involves memory and learning processes the role of the hippocampus needs to be considered, especially with respect to the memory of drug related cues and/or contexts associated with reinstatement of drug taking after a period of withdrawal (Ramirez et al., 2009). Indeed there is a persistent increase in glutamate levels in the hippocampus in mice during the initial learning phase in an operant chamber when administered a food reward (Win-shwe et al., 2009). Intra-dorsal hippocampal infusions of the mGluR1 antagonist JNJ16259685 dose dependently attenuates context-induced reinstatement of cocaine-seeking without affecting instrumental behaviour, motor activation or food reinforced behaviour. However, the same affect is not observed with infusions of the antagonist into the somatosensory cortex (Xie et al., 2010). This would implicate glutamatergic transmission within the dorsal hippocampus, mediated primarily by the highly expressed mGluR1s in this region, in the regulation of the incentive motivational and/or memory components contributing to cocaine-seeking. More recently the same authors argue that the ventral, as opposed to the dorsal, hippocampus may play a greater role in mediating these effects (Lasseter et al., 2010). Furthermore in support of the role of mGluR1s in mediating hippocampal memory and learning, mGluR1 knockout mice have impaired LTP and are unable to learn associative tasks (Gil-Sanz et al., 2008). These traits that can be mimicked in wild type animals administered a mGluR1 antagonist (Gil-Sanz et al., 2008). Overall, further clarification on the role of mGluR1s on hippocampal mediated behaviours is needed.

## 2. The ability of mGluRs to form receptor mosaics

### 2.1. Group I: mGluR1

In 1998 Kubo et al. used cultured *Xenopus laevis* oocytes to demonstrate that both mGlu1α and mGlu5 receptors are activated by not only glutamate, but also extracellular calcium levels (Kubo et al., 1998). Furthermore exposure to increased extracellular calcium levels results in a prolongation of glutamate responses in a concentration-dependent manner in hamster ovary cells expressing mGluR1α (Miyashita and Kubo, 2000a). To a lesser degree, mGluR3 was also responsive to both glutamate and extracellular calcium levels with mGluR2 only becoming activated when extracellular calcium levels were greater than would be found physiologically (Kubo et al., 1998). The authors hypothesised that the ability of mGluRs to respond to

calcium may increase the basal activity of secondary messenger systems maintaining functions such as LTP (Kubo et al., 1998). The ability of the mGluR1α to sense and be activated by calcium increases the basal cAMP levels via direct coupling with Gs. This is sufficient to trigger downstream signalling cascades resulting in changes to cellular morphology (Miyashita and Kubo, 2000b). It has been shown that mutation of the glutamate binding site on a mGlu1α receptor will abolish glutamate signalling leaving signalling in response to extracellular calcium levels intact and permitting the mGluR1α to act as solely a calcium sensing receptor. Mutating the calcium binding residues reduces the ability of mGluR1α to sense not only extracellular calcium levels but also glutamate in some cases (Jiang et al., 2010). The authors also go on to show that there is a novel calcium binding site adjacent to the glutamate binding site in the hinge region of the extracellular domain of the receptors. They propose that binding of 2 different ligands i.e. glutamate (a neurotransmitter) and calcium (a divalent cation) to their distinct, but partially overlapping binding sites synergistically modulate and potentiate mGluR1α activation of intracellular signalling to yield a maximal affect (Jiang et al., 2010). This covalent heterodimerization of mGluR1α and calcium sensing receptors occurs in select regions of the brain such as the hippocampus and cerebellum (Gama et al., 2001). Heterodimerization with calcium receptors is also observed for mGluR5 with trafficking of the receptors being regulated by Homer1c (Gama et al., 2001).

### 2.2. Group I: mGluR5

The establishment of hetero-oligomeric complexes aids in the explanation of the reciprocal affects to multiple neurotransmitter systems upon stimulation of mGluRs. For example, repeated exposure to MTEP (2 mg/kg/day over 12 days) is sufficient to reduce not only mGluR5 expression, but the expression of the mRNA for subunits of both NMDA and AMPA receptors whilst increasing dopamine receptor binding (Cowen et al., 2005). Agonists of the mGlu5 receptor increase extracellular striatal glutamate levels which can be prevented by infusing either a mGluR5 or adenosine $A_{2A}$ antagonist (Pintor et al., 2000). Whilst NMDA-receptor signalling can be facilitated via mGluR5 activation (Rosenbrock et al., 2010). Based on biochemical and co-localization studies mGluR heterodimers have been proposed to exist between mGluR5 and NDMA (Rosenbrock et al., 2010); dopamine D2 (Popoli et al., 2001); adenosine $A_{2A}$ (Ferre et al., 2002); μ-opioid (Schroder et al., 2009) or GABA(A)α1 (Besheer and Hodge, 2005) receptors. Other heterodimers have been proposed to exist between mGluR1α and calcium (Jiang et al., 2010) or oestrogen (Boulware et al., 2005) receptors. However, to date receptor dimerization has been restricted to oligomers containing only two protomers (Ferre et al., 2002). Using biomolecular fluorescence complementation, bioluminescence resonance energy transfer and sequential resonance transfer techniques Cabello et al. (2009) have recently shown that mGluRs can form higher-order oligomers in living cells. The authors not only illustrate that mGluR5s dimerize with dopamine D2 receptors, but identified complexes containing mGluR5, dopamine D2 and the adenosine $A_{2A}$ receptor illustrating that all 3 receptors may be physically linked in the cell membrane (Cabello et al., 2009). In rat striatal homogenates, receptors forming the oligomer co-distribute in post-synaptic structures along the extrasynaptic plasma membrane of the same dendritic spines of GABAergic striatopallidal neurons (Cabello et al., 2009). The authors acknowledge that they cannot rule out that this oligomer may also exist presynaptically to control the excitability of MSNs as presynaptic interactions, at least for mGluR5 and adenosine $A_{2A}$ receptors have been suggested (Rodrigues et al., 2005).

### 2.3. Group II: mGluR2/3

Unlike Group I receptors less is known about the ability of Group II receptors to form oligomeric complexes. Gonzalez-Maeso et al. (2008) have shown that mGluR2 interacts via specific transmembrane helix domains with the serotonin (5-HT) 2A receptor to form a heterodimeric complex (Gonzalez-Maeso et al., 2008), even though these two receptors are from different families of GPCRs. The authors determine that the mGluR2/5-$HT_{2A}$ complex has functional consequences as binding affinities of agonists for both mGlu2/3 and 5-$HT_{2A}$ receptors are decreased when the receptor G-protein complexes were uncoupled with GTPγS. Furthermore, the allosteric interactions observed with agonist binding were eliminated by antagonists for each receptor (Gonzalez-Maeso et al., 2008). The authors also show that LY379268 is able to suppress 5-HT mediated behaviours. Even though the authors utilise a non-selective mGluR2/mGluR3 agonist for their assays the lack of evidence for mGluR3/5-$HT_{2A}$ complexes, they suggest, would support specific mGluR2/5-$HT_{2A}$ cross talk. More recent studies have shown that LY379268 inhibits 2,5-dimethoxy-4-iodoamphetamine (DOI, a 5-$HT_{2A}$ agonist) induced polyphosphoinositide hydrolysis in both mGluR2 and mGluR3 knockout mice (Molinaro et al., 2009). This suggests that like mGluR2, mGluR3s may also regulate 5-$HT_{2A}$ mediated responses. Irrespectively these complexes may serve to integrate 5-HT and glutamate signalling via modulation of G-protein coupling and whilst current focus of these complexes is primarily related to their role in psychosis, their potential for regulating mechanisms related to drug addiction should not be ignored. Indeed, exposure to drugs of abuse increases 5-HT levels in the NAcc (Riegel et al., 2004) with 5-HT receptors in this region hypothesised to be critical for regulating drug induced neuroplasticty following protracted withdrawal. It is possible this occurs via glutamatergic processes. Intra-NAcc infusion of either a 5-$HT_{2A}$ or 5-$HT_{2C}$ antagonist is able to block locomotor activity and inhibit glutamate sensitization following a 15 mg/kg cocaine challenge in rats that have been in withdrawal for 3 weeks (Zayara et al., 2011). It is yet to be determined whether mGluR2/3s can form higher order oligomers such as those identified for Group I receptors. Pre-treatment with the AMPA receptor antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione (NBQX) attenuates the increase in dopamine to basal levels induced by antagonism of mGluR2/3 in the NAcc shell. NBQX application alone had no affect on dopamine levels (Karasawa et al., 2010). As this interaction occurs at a yet undefined level it leads way for the potential of Group II receptors to form higher order oligomers.

It is becoming increasingly evident that the mechanisms of activation of mGluRs are extremely complex. Information about whether receptors forming higher order oligomers are physically associated by direct protein coupling or via cytosolic proteins such as Homer and their resultant effects following stimulation is needed. Irrespectively, the presence of heteromeric complexes and higher-order oligomers leads way to synergistic and antagonistic interactions of different ligands at the one site to facilitate neurotransmitter release and thus the modulation of pathways. For example, co-administration of agonists and/or antagonists for mGluR5 and adenosine $A_{2A}$ receptors results in a synergistic potentiation or depressant affect on dopamine D2 mediated turning behaviours (Ferre et al., 1999; Popoli et al., 2001). Perfusion of the mGluR5 agonist (RS)-2-chloro-5-hydroxyphenylglycine (CHPG) into the NAcc increases GABA release in the ventral pallidum. This can be potentiated by the adenosine $A_{2A}$ agonist CGS 21680 and counteracted by co-infusion of the dopamine D2 agonist quinpirole (Diaz-Cabiale et al., 2002). Whilst synergistic affects of co-stimulation of the adenosine $A_{2A}$ and mGlu5 receptors is observed in extracellular signal-regulated kinase 1/2 phosphorylation and c-fos expression, there is no synergistic effect at the level of second messengers (i.e. cAMP or intracellular calcium levels) (Ferre et al., 2002). This suggests cross-talk between independent signalling pathways that converge at the levels of MAPK cascade. In addition, our lab has shown that co-administration of MTEP and the adenosine $A_{2A}$ antagonist SCH58261 at individually sub-threshold doses reduces ethanol responding and cue-induced reinstatement of ethanol-seeking (Adams et al., 2008). The same affects

are not observed between mGluR5 and adenosine $A_1$ receptors suggesting subtype receptor specificity of these interactions. We have also shown that combinations of both the cannabinoid receptor ($CB_1$) antagonist SR141716A and MTEP, or the adenosine $A_{2A}$ antagonist SCH58261 and SR141716A are able to reduce ethanol-self administration (Adams et al., 2010). However, only the combined administration of SR141716A and MTEP are sufficient to prevent cue-conditioned alcohol-seeking following abstinence, with combined application of SR141716A and adenosine $A_{2A}$ antagonists having no affect (Adams et al., 2010). This suggests receptor specific roles in the mediation of various aspects of at least alcohol related behaviours, namely attenuation of relapse compared to self-administration. Thus, interactions of mGluRs across multiple receptor oligomers may be critical for the synchronised activity and functional regulation of pathways. The potential being that synergistic activation of all receptors in the oligomer is required to achieve the most efficient response. Oligomers also provide an avenue for a combinatorial approach to therapeutics reducing the dose of an individual drug and minimising adverse side effects. However caution should be taken as pharmacological blockade of either NMDA or Group I mGluRs may have opposing affects (Wibrand et al., 2010). The question of whether receptor mosaics are derived during biosynthesis or following ligand-promoted exchanges between the receptors to regulate expression of all constituents at the cell surface is yet to be determined. Irrespectively their existence results in significant consequences for signal transduction (see Angers et al., 2002 for review). Indeed receptor oligomerization could account for unexplained pharmacological diversities. As such the understanding of these functions is increasingly important if we wish to target specific receptor complexes for intervention strategies as actions at these sites may have confounded affects on numerous transmitter systems.

### 2.4. The role of microRNAs in mGluR mediated addictive behaviours

A newly identified area of research that is of relevance to addiction is the 1993 discovery of microRNAs (miRNAs) (Lee et al., 1993). MiRNAs are short non-coding RNAs, ranging in size from 19 to 24 nucleotides. They are becoming increasingly studied due to their ability to coordinate the fine-tuning of post-transcriptional gene expression, generally acting to inhibit protein synthesis by suppressing translation or causing mRNA degradation (Jackson and Standart, 2007; Standart and Jackson, 2007; Filipowicz et al., 2008). The complexity of miRNAs is amplified by the fact that any one miRNA has multiple targets, and more than one miRNA can regulate the same mRNA. Whilst normally playing a key role during development (Lee et al., 1993) there is increasing evidence that miRNAs play a critical role in the neuroadaptations that occur in the transition from drug taking to addicted state as long-lasting synaptic plasticity requires protein synthesis (see Pietrzykowski, 2010). Indeed miRNAs play a key role in memory and learning (Konopka et al., 2010). Chemically induced LTP or Group I mGluR dependent LTD (induced by the agonist (S)-3,5-dihydroxyphenylglycine (S-DHPG)) evokes changes in the expression of numerous hippocampal miRNAs in a bidirectional manner (Park and Tang, 2009). High frequency stimulation of the medial perforant pathway increases the expression of miRNA-132 and 212 in the hippocampus, the affect of which can be abolished by local infusion of the Group I mGluR antagonist (RS)-1-aminoiindan-1,5-dicarboxylic acid (AIDA) (Wibrand et al., 2010). In this paradigm antagonism of Group 1 mGluRs is not sufficient to prevent LTP induction or maintenance, but is sufficient to block activity-dependent depotentiation of LTP. This process is strongly dependent on mGluRs regulation of miRNAs-132 and 212 rather than miRNAs regulated by NMDA receptors, as NMDA blockade had no affect (Wibrand et al., 2010). In addition miRNAs themselves are able to control glutamate receptor function (Kocerha et al., 2009) and expression (Karr et al., 2009), at least for iGluRs as postsynaptic knock-down of dicer-1(a endoribonuclease necessary for miRNA synthesis) in *Drosophila* leads to an increase in the expression of postsynaptic iGluRs (Karr et al., 2009).

Whilst miRNA/mGluR interactions appear to play a role in hippocampal mediated memory and learning, the role of miRNAs in regulating drug induced changes in the mesocorticolimbic pathway is only currently beginning to be explored. Specific miRNAs have been hypothesised to regulate the fine-tuning of dopaminergic neurons and thus dopaminergic mediated behaviours such as locomotion via a negative feedback circuit (Kim et al., 2007). They also are sufficient to alter dopamine D1 receptor expression (Huang and Li, 2009a). Drugs of abuse are able to alter gene expression via miRNA mediated pathways (Chandrasekar and Dreyer, 2009; Huang and Li, 2009b), with miRNAs being implicated in mediating the affects of nicotine (Huang and Li, 2009b) and alcohol (see Miranda et al., 2010; Pietrzykowski, 2010 for extensive review). Furthermore, their increased expression has been suggested to contribute to alcohol tolerance (Pietrzykowski et al., 2008). Extended access to cocaine increases the expression of both miRNA-132 and 212 in the dorsal striatum leading to downstream consequences on signalling pathways including CREB (Hollander et al., 2010). Interestingly, using Lentivirus the authors show that over expression of striatal miRNA 212 specifically decreases the motivation of animals to self-administer cocaine, whilst inhibiting miRNA 212 using anti-sense oligonucleotides increases cocaine intake in extended access rats (Hollander et al., 2010). The authors suggest that striatal miRNA 212 expression is protective against the development of compulsive drug taking illustrating the intracellular pathways that may be involved and suggest that deficits in miRNA 212 signalling may increase an individual's vulnerability to addiction (Hollander et al., 2010; Im et al., 2010). Chronic cocaine treatment has been shown to induce alterations in the expression (both up and down) of miRNAs in a miRNA and region specific manner (Chandrasekar and Dreyer, 2009). In the same animals the expression of the miRNA's 124 and Let 7d are down regulated in the VTA and hippocampus whilst miRNA 181a is increased in the NAcc and hippocampus following cocaine. Lenti virus-mediated over expression of miRNA 124 and Let 7d results in a miRNA specific effect on mRNA/protein expression; over expression of miRNA 124 results in a down regulation of BDNF, whilst over expression of Let 7d results in a down regulation of the dopamine D3 receptor (Chandrasekar and Dreyer, 2009). Over expression of miRNA 181a, which has a predicted high binding to mGluR5 and AMPA Glu2 glutamate receptors, as well as Homer 1, was not assessed. Thus, the authors show that cocaine has differential and specific effects on gene regulation and that via feedback loops miRNA's regulate the expression of proteins involved in synaptic plasticity in addiction related pathways. The group have also gone on to show that the expression of these same miRNAs in the NAcc is sufficient to either attenuate (miRNA 124 and Let 7d) or enhance (miRNA 181a) cocaine-induced CPP (Chandrasekar and Dreyer, 2011). Dendritic spine morphology has been shown to be regulated by BDNF/miRNA 134/LimK1 interactions, at least in hippocampal neurons (Schratt et al., 2006). Kawashima et al. (2010) report that in cortical neurons BDNF stimulates an upregulation of miRNA 132 specifically and not miRNAs 134 or 124 and that miRNA 132 is able to regulate, at least, ionotropic glutamate receptors (Kawashima et al., 2010). To date the only evidence showing a relationship between drug intake and altered miRNA induced mGluR expression is for mGlu7 receptors (Zhou et al., 2009) and it is yet to be determined whether striatal changes in miRNAs are mediated by mGluRs as seen in the hippocampus. It is possible that drug induced modulation of miRNAs could result in enhancement or silencing of genes critical for the induction of learning and memory and the maintenance of addictive behaviours. However, the influence of miRNAs regulation of mGluR mediated protein expression in this process requires clarification.

## 3. Concluding remarks

This review encompasses the work over the last few years that advance our understanding of how mGluR activation results in

enduring affects on addictive behaviours. Imbalances in glutamate transmission primarily in the corticostriatal and limbic pathways following exposure to drugs of abuse appear to play a key role in mediating synaptic plasticity pertinent to addiction. As a consequence drug-seeking behaviours are maintained leading to the incidence of relapse even after protracted abstinence (Jupp et al., 2011). This appears, in part, dependent on the ability to impair LTD in regions associated with addictive behaviours such as the NAcc. Both Group I and Group II mGluRs may have a role in mediating these neuroadaptations, though the mechanism via which these affects occur appear subunit specific and dependent on influences from intracellular and molecular components such as Homer proteins and miRNAs. In addition, the widespread distribution of mGluRs and the evidence for receptor mosaics give rise to the possibility of synergistic affects of mGluR activation across multiple neurotransmitter systems adding to the complexity of intervention strategies to improve behavioural outcomes. Thus, the complex and diverse roles mGluRs play in modulating the highly intertwined network of neurotransmitter systems involved in addiction, makes them a complex but intriguing avenue for future research.

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