The Receptors

Richard Teke Ngomba
Giuseppe Di Giovanni
Giuseppe Battaglia
Ferdinando Nicoletti *Editors*

# mGLU Receptors

Humana Press

# The Receptors

Volume 31

**Series Editor**

Giuseppe di Giovanni
Department of Physiology & Biochemistry
Faculty of Medicine and Surgery
University of Malta
Malta, Italy

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Giuseppe Battaglia • Ferdinando Nicoletti
Editors

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*Editors*
Richard Teke Ngomba
Neuropharmacology Unit I.N.M. Neuromed
I.N.M. Neuromed
Pozzilli, Isernia, Italy

Giuseppe Battaglia
Neuropharmacology Unit
I.N.M. Neuromed
Pozzilli, Isernia, Italy

Giuseppe Di Giovanni
Department of Physiology and Biochemistry
University of Malta
Malta, Italy

Ferdinando Nicoletti
Dipartimento di Fisiologia Umana
Università di Roma
Roma, Italy

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# Preface

Metabotropic glutamate (mGlu) receptors have been discovered in the mid-1980s by a French group of scientists (Sladeczek et al., Nature, 1985), who include some of the current leaders in the field. Since then, the field has grown exponentially, and now subtype-selective ligands of mGlu receptors [orthosteric agonists and antagonists, positive and negative allosteric modulators (PAMs and NAMs), and agonists/PAMs] are under development for the treatment of neurological and psychiatric disorders. The present book is the follow-up of the 8th International Meeting on Metabotropic Glutamate Receptors (Taormina, Italy, 2014) and incorporates chapters from some of the authorities in the mGlu receptor field.

The chapter by Philippe Rondard, Xavier Rovira, Cyril Goudet, and Jean-Philippe Pin is the state of the art of mechanisms regulating the structural and functional dynamics of mGlu receptors and their relevance to mGlu receptor pharmacology. This group of scientists has highly contributed to our current knowledge of physical interactions (homo- and heterodimerization) and allosteric modulation of mGlu receptors. Recent findings obtained by the authors and their collaborators lay the groundwork for the development of light-regulated ligands of mGlu receptors (i.e., drugs that can be either activated or inactivated by light). These molecules represent new valuable tools for the study of the role played by individual mGlu receptor subtypes in physiology and pathology with a high spatial and temporal resolution. Some of these drugs have recently appeared in the literature and hold promise for the treatment of pain and anxiety.

The chapter by Hardy Hagena and Denise Manahan-Vaughan is an excellent synopsis of the role played by mGlu receptors in mechanisms of hippocampal synaptic plasticity underlying information processing and long-term memory. This is a theme of great relevance from a therapeutic standpoint considering that some mGlu receptor ligands (e.g., mGlu5 receptor PAMs and mGlu2 receptor NAMs) are under development as cognition enhancers. In vivo studies on synaptic plasticity performed in Denise's lab are milestones in the mGlu receptor field.

The chapter by Zhengping Jia and Graham Collingridge focuses on mechanisms underlying mGlu receptor-dependent long-term depression (LTD) of excitatory synaptic transmission, a particular form of activity-dependent synaptic plasticity

that has attracted the interest of scientists working on fragile X and other forms of monogenic autism. Graham is an absolute authority in the field of synaptic plasticity. The authors discuss the role played by the GluA2 subunit of AMPA receptors in mGlu receptor-dependent LTD proposing a molecular model that links functional and structural plasticity through molecular events mediating actin remodeling.

Three chapters by (i) Paolo Gubellini, Yoland Smith, and Marianne Amalric; (ii) Gunasingh Masilamoni and Yoland Smith; and (iii) Nicolas Morin and Therese di Paolo focus on the role played by mGlu5 receptors in the pathophysiology of Parkinson's disease (PD) and L-DOPA-induced dyskinesias (LIDs). These chapters highlight the importance of translation research in the mGlu field describing how data obtained in preclinical models (e.g., 6-hydroxydopamine-treated rats and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated mice and monkeys) laid the groundwork for clinical studies with mGlu5 receptor NAMs in patients with PD and LIDs. Of note, mGlu5 receptor NAMs not only produce symptomatic benefit in PD and LIDs but also exert neuroprotective effects in "parkinsonian" mice and monkeys, suggesting that these drugs cater the potential to behave as disease modifiers.

The chapter by Javier Gonzalez-Maeso is a nice synopsis of the epigenetic and functional mechanisms regulating the cross talk between mGlu2 and 5-$HT_{2A}$ receptors. This mechanism, which has been described in detail in some seminal papers by Javier and his collaborators, is of great relevance to the pathophysiology and treatment of schizophrenia.

The chapter by Francesco Ferraguti focuses on mGlu receptors in the amygdala, a complex brain structure that plays a key role in fear memory and anxiety. Francesco is one of the best neuroanatomists and pharmacologists in Europe, and he is highly contributing to our current knowledge of the complex neuronal circuits linking the input and output nuclei of the amygdaloid complex.

The chapter by Tom Salt and Carolina Copeland examines the role played by mGlu receptors in the regulation of synaptic transmission in the thalamus. Tom Salt's lab is pioneer in the study of thalamic function in response to sensory inputs.

The chapter by Gilles van Luijtelaar, Valerio D'Amore, Ines Santolini, and Richard Ngomba focuses on mGlu5 receptors as a new candidate drug target for the treatment of absence epilepsy. Absence seizures are characterized by spike-and-wave discharges at the EEG, which are generated by an abnormal oscillatory activity within a cortico-thalamic-cortical circuit. A significant percentage of patients with absence epilepsy is refractory to current medication. mGlu5 receptor PAMs hold promise as new drugs for the treatment of absence epilepsy and may act in the thalamus by restraining GABAergic transmission.

The chapter by Francesca Guida, Enza Palazzo, L. Longo, Ida Marabese, Vito de Novellis, and Sabatino Maione examines the role played by mGlu receptors in the pain pathways focusing on supraspinal mechanisms. Supraspinal mechanisms are involved in the top-down regulation of pain transmission and mediate the affective and cognitive aspects of pain, being a linking bridge between chronic pain and affective disorders. Dino Maione's group is leader in the study of mGlu receptors and pain regulation.

The chapter by Andrew Lawrence and Christina Perry focuses on mGlu receptors as candidate drug targets for the treatment of drug addiction. Several lines of evidence indicate that mGlu5 receptor NAMs inhibit both drug taking and drug seeking. Here, the authors comment on mGlu5 receptors and drug addiction from a different angle. Moving from the evidence that mGlu5 receptors contribute to mechanisms of activity-dependent synaptic plasticity, Andrew and Christina suggest that mGlu5 receptor PAMs may serve as useful add-on treatment to behavioral therapy in addiction.

Finally, the chapter by Suzy Chen is a nice synopsis of what we currently know about mGlu receptors and cancer and focuses on the link between mGlu1 receptors and the pathophysiology of malignant melanomas. Melanoma is one of the most aggressive tumors originating from melanocytes, which are cells present in the skin, uvea, and leptomeninges and originate from the neural crest. Although the current use of BRAF and MEK inhibitors and immunotherapies has extended the progression-free survival and overall survival of patients, the treatment of metastatic melanomas is still suboptimal. Suzy Chen and her collaborators have demonstrated that ectopic expression of mGlu1 receptors in melanocytes is sufficient to generate melanomas in mice and that human melanoma samples and melanoma cell lines express mGlu1 receptors. Riluzole, a drug that lowers the concentrations of ambient glutamate, limits the growth of melanomas and shows radio-sensitizing activity in the treatment of brain metastasis of melanoma. This paves the way to the clinical use of drugs that restrain the activation of mGlu1 receptors as adjunctive treatment in patients with melanoma.

In conclusion, this is an excellent book that is easy to read and critically reviews some of the most relevant aspects related to the physiology and pharmacology of mGlu receptors.

Isernia, Italy — Richard Teke Ngomba, Pharm.D., Ph.D.
Msida, Malta — Giuseppe Di Giovanni, Ph.D.
Isernia, Italy — Giuseppe Battaglia, M.D., Ph.D.
Roma, Italy — Ferdinando Nicoletti, M.D., Ph.D.

# Contents

# Chapter 1
# mGlu5 Signaling: A Target for Addiction Therapeutics?

**Christina J. Perry, M. Foster Olive, and Andrew J. Lawrence**

**Abstract** The role of metabotropic glutamate 5 (mGlu5) receptors in substance abuse disorders has been a focus of research for over a decade. In animal models, mGlu5 antagonists not only decrease drug taking but also drug seeking. It follows that mGlu5 antagonists are promising potential pharmacotherapeutic agents for the treatment of substance abuse. More recently, however, evidence has emerged that such compounds may in fact interfere with cognitive behavioral strategies for treatment of such disorders. mGlu5 receptors are linked to N-methyl-D-aspartate (NMDA) receptors via scaffold proteins and consequently are critical for NMDA receptor-dependent neural plasticity, giving them a prominent role in learning and memory. This is important because these processes are critical for rehabilitation treatment during recovery from substance abuse disorders. Therefore, although an antagonist or negative allosteric modulator (NAM) for mGlu5 may serve to decrease the reinforcing value of drugs such as cocaine or methamphetamine, it may also interfere with the process of behavioral change during treatment. Conversely, mGlu5 stimulation may actually serve to enhance this process. This chapter will follow the line of evidence supporting the idea that compounds that enhance mGlu5 receptor function may serve as useful adjuncts to behavioral therapy for substance abuse. We will also discuss the effects of chronic drug use on mGlu5 expression and function. We propose that mGlu5 PAMs in fact show promise as short-term adjuncts to behavioral therapy and could improve the long-term prognosis of such strategies.

**Keywords** Metabotropic glutamate 5 • Addiction • Cognition • Learning • Memory • Reinforcement • Treatment • Negative allosteric modulator • Positive allosteric modulator

C.J. Perry, Ph.D. (✉) • A.J. Lawrence, Ph.D., FBPhS
Behavioural Neuroscience Division, Florey Institute of Neuroscience and Mental Health, 30 Royal Parade, Parkville, VIC 3052, Australia
e-mail: Christina.perry@florey.edu.au; Andrew.lawrence@florey.edu.au

M.F. Olive, Ph.D.
Behavioral Neuroscience Area, Department of Psychology, Arizona State University, Tempe, AZ, USA
e-mail: foster.olive@asu.edu



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## Abbreviations

| | |
|---|---|
| CDPPB | 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide |
| CET | cue exposure therapy |
| LTD | long-term depression |
| LTP | long-term potentiation |
| mGlu5 | metabotropic glutamate 5 |
| MPEP | 2-Methyl-6-(phenylethynyl)pyridine |
| MSN | medium spiny neuron |
| MTEP | 3-((2-Methyl-4-thiazolyl)ethynyl)pyridine |
| NAM | negative allosteric modulator |
| NMDA | N-Methyl-D-aspartate |
| PAM | positive allosteric modulator |

## 1.1 Introduction: Pharmacotherapy and Allosteric Modulators

In recent years there has been increasing interest in the potential for allosteric modulators of the metabotropic glutamate 5 (mGlu5) receptor to be used in the treatment of a number of different disorders. Targeting metabotropic rather than ionotropic receptors is regarded as a safer strategy because it avoids unwanted side effects that arise from suppression of fast glutamatergic excitatory transmission (Carroll 2008). Likewise, allosteric modulators have increased receptor selectivity and fewer contraindications than agonists or antagonists that bind to the orthosteric binding site (Carroll 2008; Nickols and Conn 2014). Such favorable characteristics result from these compounds having no intrinsic agonist or antagonist ability but rather an influence over receptor activity only when the endogenous agonist itself is present (Gregory et al. 2011). This, however, is not to say that they are free of side effects. mGlu5 negative allosteric modulators (NAM) at high doses can induce psychotomimetic effects and cognitive impairments in animal models (Campbell et al. 2004) and in clinical trials (Pecknold et al. 1982; Friedmann et al. 1980), while positive allosteric modulators (PAMs) at high doses can induce seizures (Nickols and Conn 2014). Nevertheless, such improvements in drug development have allowed for mGlu5 NAMs to be tested at the clinical trial phase and beyond for a number of different disorders, including anxiety, depression, Parkinson's disease, and Fragile X syndrome (Gregory et al. 2011), while PAMs might be useful for treating schizophrenia (Nickols and Conn 2014; Gregory et al. 2011).

Substance abuse is an area of mental health where there is a pressing need for novel and effective medication (Kim and Lawrence 2014; Douaihy et al. 2013), and increasingly it seems that mGlu5 allosteric modulators are promising candidates (Gregory et al. 2011; Olive 2010; Bird and Lawrence 2009). However, there is

conflicting evidence as to how best to apply these treatments to achieve long-term resistance to relapse. On the one hand, mGlu5 NAMs may reduce the reinforcing properties of drugs of abuse (Watterson et al. 2013; Keck et al. 2013; Kumaresan et al. 2009) and, as a consequence, the severity of an acute relapse episode. On the other, an mGlu5 PAM has the potential to act as a cognitive aid (Olive 2010; Homayoun and Moghaddam 2010), facilitating behavioral therapy and creating longer-term cognitive resistance to relapse. The purpose of this chapter is to review the evidence for both of these possibilities and evaluate the most effective strategy (in theory) for treating substance abuse using mGlu5 allosteric modulators.

## 1.2 Negative Allosteric Modulators Reduce Drug Reward

It has been reported that mice lacking the mGlu5 receptor show decreased sensitivity to the rewarding and locomotor-stimulating properties of cocaine and morphine (Chiamulera et al. 2001; Veeneman et al. 2011), although these findings have not been replicated with regard to cocaine (Bird et al. 2014). Nevertheless, NAMs reduce behavioral sensitization to cocaine (McGeehan and Olive 2003; Scheggi et al. 2007; Brown et al. 2012; Martinez-Rivera et al. 2013), alcohol (Kotlinska et al. 2006), and amphetamine (McGeehan et al. 2004). mGlu5 NAMs increase the threshold for intracranial self-stimulation (ICSS), which indicates a decrease in brain reward function (Kenny et al. 2005; Cleva et al. 2012). Likewise, mGlu5 NAMs reduce perseveration for drug reinforcement in a progressive ratio test (Paterson and Markou 2005). Together, these findings suggest a role for mGlu5 receptors in the reinforcing and motivational properties of addictive drugs.

A medication that can reduce the motivation to seek drugs is certainly a desirable candidate for substance abuse treatment for drug addiction. Indeed, in preclinical models of relapse, mGlu5 NAMs reduce drug-primed reinstatement of drug seeking for cocaine (Kumaresan et al. 2009; Wang et al. 2013; Schmidt et al. 2014), ethanol (Backstrom et al. 2004), or methamphetamine (Watterson et al. 2013). In addition, reinstatement triggered by drug-associated cues (Wang et al. 2013; Backstrom and Hyytia 2006; Martin-Fardon et al. 2009) or contexts (Knackstedt et al. 2014) is also reduced following administration of an mGlu5 NAM. These findings are promising, because they indicate that NAMs might reduce the severity of an acute relapse episode, and also decrease craving and motivation to seek drug in recovering addicts.

There are, however, some important impediments to application of mGlu5 NAMs for treating substance abuse. First, there is evidence that tolerance to these compounds can develop quite quickly (Cleva et al. 2012). This is critical, because effective medication with a NAM would involve a long-term prescription to avoid potential negative ramifications of exposure to drugs or drug-associated cues and future time points undefined. Therefore, it is quite possible that the protection afforded by the medication would lessen over time. Second, mGlu5 receptor expression changes following increased drug exposure. Given that much of the data discussed above derives from preclinical models where there is only limited exposure

to drug, it may be that they are not directly applicable to the case of substance abuse clients, who by definition have had extended exposure to the drug in question. Indeed, we will describe how changes to mGlu5 receptor availability have been documented in cocaine and nicotine addicts undergoing withdrawal (Martinez et al. 2014; Milella et al. 2014; Hulka et al. 2014). Finally, mGlu5 NAMs have negative impact on cognitive function (Campbell et al. 2004), in particular to memory formation (Naie and Manahan-Vaughan 2004; Rodrigues et al. 2002; Simonyi et al. 2010; Homayoun et al. 2004), spatial learning (Manahan-Vaughan and Braunewell 2005; Christoffersen et al. 2008; Petersen et al. 2002), and inhibitory learning (Kim et al. 2014; Xu et al. 2009). This last point is a critical consideration because there is ample evidence that cognitive capacity is positively correlated with treatment outcome for substance abuse disorders (e.g. Aharonovich et al. 2006). Decreased mGlu5 function is associated with extinction deficits (Bird et al. 2014; Kim et al. 2014; Chesworth et al. 2013), and extinction forms an integral part of many behavioral strategies targeting addiction (Conklin and Tiffany 2002). Therefore there is a very good chance that, although mGlu5 NAMs may offer acute benefits in the form of reducing the reinforcing properties of addictive drugs, they may simultaneously create long-term cognitive impairments that interfere with behavioral therapy, hence ultimately increasing the likelihood of future relapse. These issues will be addressed in the following sections.

## 1.3 mGlu5 Receptors and Synaptic Plasticity

mGlu5 receptors are widely distributed throughout the mammalian brain (Shigemoto and Mizuno 2000), with highest levels of expression in forebrain regions such as the cerebral cortex, dorsal and ventral striatum, olfactory bulb and tubercle, lateral septum, and hippocampus (Shigemoto et al. 1993; Romano et al. 1995). Within these regions, mGlu5 receptors are predominantly expressed on postsynaptic elements, particularly the perisynaptic annulus of dendritic spines (Shigemoto and Mizuno 2000), although some investigators have reported localization of mGlu5 receptors to presynaptic terminals and glia (Mitrano and Smith 2007; Anwyl 1999).

mGlu5 receptors are integral to both the initiation and maintenance of synaptic plasticity in the form of long-term potentiation (LTP) or depression (LTD) of synaptic efficacy. This is achieved via a variety of subcellular signaling mechanisms including facilitation of N-methyl-D-aspartate (NMDA) receptor function, interactions with postsynaptic scaffolding proteins, release of calcium into the cytosol from the endoplasmic reticulum, and resulting activation of downstream effector proteins such as MAP and ERK kinases which in turn activate transcription factors to modulate gene expression and initiation of phospholipid signaling (Anwyl 2009; Bellone et al. 2008; Gladding et al. 2009). Perhaps the most widely studied and understood mechanism for mGlu5-mediated enhancement of LTP is via positive coupling of these receptors to postsynaptic NMDA receptor function (Alagarsamy et al. 2001; Attucci et al. 2001; Awad et al. 2000; Benquet et al. 2002; Doherty et al. 1997; Kotecha and MacDonald 2003; Pisani et al. 2001; Ugolini et al. 1999), which is

largely mediated by mGlu5-induced activation of PKC and phosphorylation of (among other substrates) specific subunits of the NMDA (Lu et al. 1999). In addition to these biochemical interactions, there is also evidence for interactions between mGlu5 and NMDA receptors that are either direct or indirect via various scaffolding proteins including PSD-95, Shank, and the Homer family of proteins (Perroy et al. 2008; Hermans and Challiss 2001). mGlu5 receptors also regulate the synthesis of retrograde signaling molecules such as endocannabinoids, which stimulate presynaptic $CB_1$ receptors to initiate LTD (Bellone et al. 2008).

## 1.4 mGlu5 Receptor Expression Changes Across Development of Addiction

Many of the animal models used to investigate the role of mGlu5 in drug seeking and drug taking involve animals with only limited drug exposure. Models such as the extinction-reinstatement paradigm are useful for studying relapse because they encompass well the types of situations that trigger relapse in human addiction (Bossert et al. 2013). They do not, however, reflect the types of compulsive behaviors that are characteristic of long-term substance abuse. In fact, it is frequently not viable to study true addiction using animal models, because only a small percentage of those animals that are exposed to drugs will go onto develop addiction as judged by diagnostic criteria (Piazza and Deroche-Gamonet 2013), meaning that the number of experimental animals to model such behaviors would be greatly inflated.

Studying the behavior of nondependent animals provides important insights into mechanisms that lead to the development of addiction and addictive-like behavior (Bossert et al. 2013). However, it is important to remember that neural chemistry changes with increasing drug exposure, and this should be factored in when evaluating potential medications for use with substance abuse. We described previously how preclinical models have shown that mGlu5 NAMs reduce the reinforcing properties of drugs and drug-associated cues. It is also clear that chronic drug exposure causes glutamate receptor redistribution and that this affects the responsiveness of drug-seeking behavior to compounds that modulate mGlu5 receptor activity (McCutcheon et al. 2011).

These differences are apparent in models of escalated drug use, such as the long-access paradigm where laboratory animals are provided with extended opportunity to self-administer drug each day (Ahmed 2012). For example, the mGlu5 NAM MTEP decreased motivation to seek cocaine only after short but not after escalated self-administration (Hao et al. 2010). Furthermore, it was shown that an mGlu2/3 receptor agonist was more effective than MTEP in reducing ethanol seeking in dependent rats when compared with nondependent rats (Sidhpura et al. 2010). This suggests that while mGlu5 receptors mediate the incentive properties of addictive drugs during early use, following extended and escalated drug use, drug seeking may become less dependent on this receptor. In other words, treatment with an mGlu5 NAM may be ineffective against the type of behavior that will likely be in play in addicts.

Withdrawal from substance abuse also influences mGlu5 expression. In the prefrontal cortex (PFC), mGlu5 expression was reduced in rats following escalated cocaine self-administration followed by withdrawal from the drug. This difference appeared after rats were exposed to cocaine-associated cues and was correlated with the intensification of cue-induced drug seeking that occurs in cocaine-experienced animals following a period of abstinence (Ben-Shahar et al. 2013). After extended withdrawal from escalated cocaine self-administration, there is also a switch from mGlu5- to mGlu1-regulated synaptic rectification in accumbal medium spiny neurons (MSNs) (McCutcheon et al. 2011).

Changes in mGlu5 sensitivity after withdrawal are also apparent in human drug users. For example, fMRI revealed a decrease in mGlu5 availability in key cortical and limbic regions in abstinent cocaine users (Martinez et al. 2014; Milella et al. 2014), and in abstinent smokers (Hulka et al. 2014), which magnified with increasing length of abstinence (Milella et al. 2014). Thus, it seems that, although mGlu5 NAMs reduce drug seeking and relapse in animal models where there is only limited drug exposure, it is likely that they may be less efficient following escalated drug taking and withdrawal, a pattern that is typical in addicts seeking treatment. This would greatly decrease their value as medications.

## 1.5 Cognitive Capacity Is Positively Correlated with Treatment Outcome for Substance Abuse Disorders

Current behavioral treatments for addiction show poor prognosis, with roughly 60% relapsing in the first year after treatment (Conklin and Tiffany 2002; McLellan et al. 2000), and there is a strong correlation between cognitive function and treatment outcome (Aharonovich et al. 2006; Fox et al. 2009; Turner et al. 2009). This relationship most likely derives from the fact that there is an important cognitive component to treatment. Standard behavioral treatment for drug addiction consists of single or group psychotherapy (Douaihy et al. 2013). This involves assimilation of new information; hence, cognitive capacity is an important determinant of treatment outcome. In addition, many behavioral treatments involve learning new responses to drug-associated cues. This may take the form of extinction learning, such as in cue exposure therapy, where repeated presentation of previously drug-associated stimuli in the absence of further drug reward leads to a decrease in cue reactivity (i.e. craving), in abstinent substance abuse clients (Conklin and Tiffany 2002). Another, more novel approach is to provide reinforcement for abstinence behavior (Higgins et al. 2012; Silverman et al. 2012). Although these approaches are quite distinct in the way they seek to change behavior, all share the common feature of integrating new learning to implement more adaptive behavioral patterns.

Given that decline in cognitive function is in fact a well-documented consequence of long-term exposure to drugs of abuse (Fox et al. 2009; Crews and Boettiger 2009), overcoming the cognitive dysfunction that arises as a direct consequence of addiction should be a priority in therapeutic strategies to help prevent relapse. In the next section, we will describe how mGlu5 NAMs are problematic in

this regard, because they actually have the tendency to produce cognitive deficits (Campbell et al. 2004). On the other hand, mGlu5 PAMs such as CDPPB have been shown to reverse cognitive deficits produced by phencyclidine (PCP) (Horio et al. 2013) and after adolescent alcohol exposure (Gass et al. 2014).

## 1.6 Amnestic Effects of mGlu5 Inactivation

Given the established role of mGlu5 in synaptic plasticity under normal physiological conditions, it is not surprising that genetic or systemic pharmacological blockade of mGlu5 receptors attenuates the expression of LTP and LTD in regions such as the hippocampus (dentate gyrus and CA1 region), amygdala, and dorsal and ventral striatum, with concomitant deficits in various forms of learning and memory (Homayoun and Moghaddam 2010; Naie and Manahan-Vaughan 2004; Rodrigues et al. 2002; Homayoun et al. 2004; Manahan-Vaughan and Braunewell 2005; Christoffersen et al. 2008; Xu et al. 2009; Alagarsamy et al. 2001; Attucci et al. 2001; Awad et al. 2000; Benquet et al. 2002; Doherty et al. 1997; Kotecha and MacDonald 2003; Pisani et al. 2001; Ugolini et al. 1999; Bikbaev et al. 2008; Lu et al. 1997). Studies utilizing site-specific microinjections of mGlu5 NAMs including 2-methyl-6-(phenylethynyl)-pyridine (MPEP) and 3-[2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) have confirmed a critical role for these receptors in spatial navigation, inhibitory avoidance, and instrumental and/or habit learning (Rodrigues et al. 2002; Simonyi et al. 2010; Packard et al. 2001; Jacob et al. 2009). Deficits in acquisition, but not expression of a spatial learning task, were also observed following targeted knockdown of mGlu5 receptors in the mouse dorsal hippocampus (Tan et al. 2015). However, it should be noted that other laboratories have not found spatial learning memory impairments following administration of mGlu5 antagonists (Petersen et al. 2002; Semenova and Markou 2007), and some studies have indicated that mGlu5 antagonists selectively impair reference but not working memory (Naie and Manahan-Vaughan 2004; Gravius et al. 2008).

## 1.7 Facilitatory Effects of mGlu5 Activation on Learning, Memory, and Extinction Processes

In the context of behavior modification, extinction can be defined as the targeted reduction of specific maladaptive responses or behaviors, including pathological fear, anxiety, or avoidance, as well as excessive seeking of rewarding or reinforcing stimuli such as drugs of abuse. Extinction is a form of new and active inhibitory learning (Bouton 2000) and thus engages the neural mechanisms responsible for synaptic plasticity and learning and memory, including mGlu5 receptors. This is supported by findings that genetic deletion or pharmacological inhibition of mGlu5 receptors results in decrements in the extinction of conditioned fear (Handford et al. 2014) as well as cocaine and methamphetamine seeking (Kim et al. 2014; Chesworth et al. 2013).

In agreement with this, it has recently been established that PAMs selective for mGlu5, such as 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB), 4-nitro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (VU-29), and (S)-(4-fluorophenyl)-(3-[3-(4-fluorophenyl)-[1,2,4]-oxadiazol-5-yl]piperidin-1-yl)methanone (ADX47273) facilitate the induction of various markers of synaptic plasticity including long-term synaptic potentiation (Kroker et al. 2011; Ayala et al. 2009) and increased phosphorylation of the NR1 and NR2B subunits of the NMDA receptor, the GluR1 subunit of the AMPA receptor, and activate α-calmodulin-dependent kinase II, CREB, and ERK (Uslaner et al. 2009; Liu et al. 2008). Many of these effects can be blocked by NMDA antagonists, confirming that increased NMDA receptor functioning is necessary for mGlu5 PAM-induced synaptic potentiation (Ayala et al. 2009). However, interestingly, it has recently been reported that newer mGlu5 PAMs with biased agonist properties can produce pro-cognitive effects that are independent of indirect NMDA receptor activation (Rook et al. 2015).

Consistent with the notion of mGlu5 PAMs as enhancers of synaptic plasticity, these ligands have been shown to improve spatial memory in normal animals (Ayala et al. 2009; Balschun et al. 2006; Fowler et al. 2013) and reverse pharmacologically induced impairments in object recognition (Uslaner et al. 2009; Reichel et al. 2011), conditioned avoidance (Schlumberger et al. 2010; Spear et al. 2011), reversal learning (Xu et al. 2013; LaCrosse et al. 2015; Darrah et al. 2008), and five-choice serial reaction time tests (Liu et al. 2008). Many of these pro-cognitive effects of mGlu5 PAMs appear to be mediated by increased prefrontal cortical functioning (Homayoun and Moghaddam 2006, 2010; Gass et al. 2014; Stefani and Moghaddam 2010).

In the context of drug addiction, mGlu5 PAMs facilitate the extinction of a cocaine-induced conditioned place preference (Gass and Olive 2009) and reduce extinction responding following intravenous cocaine and methamphetamine and oral alcohol self-administration (Gass et al. 2014; Cleva et al. 2011; Kufahl et al. 2012). However, CDPPB failed to facilitate extinction of methamphetamine seeking when extinction sessions were conducted in a context different to the methamphetamine self-administration context (Widholm et al. 2011). Importantly, while one study reported that mGlu5 PAMs produce excitotoxicity at high doses (Parmentier-Batteur et al. 2014), others have shown that repeated mGlu5 PAM administration at more moderate doses does not produce evidence of neurotoxicity (Gass and Olive 2009) and is devoid of effects on brain reward function (Cleva et al. 2012). Thus, mGlu5 receptor PAMs may be a novel class of compounds by which to facilitate the extinction of drug stimuli or drug-context associations.

## 1.8 Conclusion

A drug that reduces the severity of a relapse episode presents an enticing therapeutic potential for addiction treatment. This is made all the more so in the case of an mGlu5 NAM because these drugs are already in clinical trials or approved for use with other disorders. However, mGlu5 receptors are integral to both the initiation and maintenance of synaptic plasticity (Alagarsamy et al. 2001; Attucci et al. 2001;

Awad et al. 2000; Benquet et al. 2002; Doherty et al. 1997; Kotecha and MacDonald 2003; Pisani et al. 2001; Ugolini et al. 1999), and this relationship affords these receptors an important role in cognitive capacity, learning, and memory. They consequently play a critical role in assimilating information and updating memories following new experiences and changes to the environment (Qi et al. 2013). Behavioral therapy for substance abuse is focused around learning new and more adaptive responses to replace drug-seeking behaviors. Whether this involves behavioral extinction or some other type of training, the need to assimilate new information is a central tenet to this process. In this regard, mGlu5 NAMs represent a "double-edged sword" – simultaneously reducing drug-seeking responses acutely while interfering with cognitive load involved in behavioral therapy. On the other hand, the pro-cognitive properties of PAMs facilitate change in animal models of behavioral therapy. Given that tolerance to the reward-reducing properties of a NAM can develop following repeat administration, and further that they are less effective in animals with more extensive drug experience, we propose that short-term application of a PAM in conjunction with behavioral therapy should in theory at least be a more effective way of treating substance abuse in the long term than a medication that has acute effects on the reinforcing effects of drug (i.e., NAM).

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# Chapter 2
# Supraspinal Metabotropic Glutamate Receptors: An Endogenous Substrate for Alleviating Chronic Pain and Related Affective Disorders

**Francesca Guida, Enza Palazzo, Livio Luongo, Ida Marabese, Vito de Novellis, Sabatino Maione, and Francesco Rossi**

**Abstract** Metabotropic glutamate receptors (mGluRs) are key players in modulating excitatory transmission and important regulators of synaptic plasticity. mGluRs are G-protein-coupled receptors (GPCRs) that have been subdivided into three groups (mGluR1–mGluR8) based on sequence homology, intracellular pathways, and pharmacological profile. mGluRs are widely localized all along the nociceptive neuroaxis, including brain circuits controlling pain often overlapping those controlling affective/cognitive behaviors which prove deeply altered in several neurological disorders including chronic pain.

This chapter summarizes current outcomes related to the supraspinal mGluRs in chronic pain states. Due to their wide expression within the pain descending system, a particular highlighting will be given to the pharmacological manipulation of mGluRs in PAG-RVM pathway, a key circuitry of the pain descending system. The current development of novel subtype-selective mGluR positive and negative allosteric modulators will allow a more stringent assessment of each mGluR subtype role in controlling chronic pain and pain-related affective cognitive behavior.

**Keywords** Metabotropic glutamate receptors • Chronic pain • Antinociceptive descending pathway • Positive and negative allosteric modulators • Pain-related affective and cognitive disorders

F. Guida, Ph.D. • E. Palazzo, Ph.D. • L. Luongo, Ph.D. • I. Marabese, Ph.D.
V. de Novellis, Ph.D. • S. Maione, Ph.D. (✉) • F. Rossi, Ph.D.
Department of Experimental Medicine, Section of Pharmacology L. Donatelli,
Università degli Studi della Campania "Luigi Vanvitelli", 80138 Naples, Italy
e-mail: franc.guida@gmail.com; enza.palazzo@unicampania.it; livio.luongo@gmail.com;
ida.marabese@unicampania.it; vito.denovellis@unicampania.it;
sabatino.maione@unicampania.it; francesco.rossi@unina2.it



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## Abbreviations

| | |
|---|---|
| BLA | basolateral amygdala |
| CeA | central nucleus of the amygdala |
| CNS | central nervous system |
| CPCCOEt | 7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxylate ethyl ester |
| (S)-3,4-DCPG | (S)-3,4-dicarboxyphenylglycine |
| GPCRs | G-protein coupled receptors |
| iGluR | ionotropic glutamate receptor |
| IL | infra-limbic |
| mGluR | metabotropic glutamate receptor |
| MPEP | 2-methyl-6-(phenylethynyl)pyridine |
| mPFC | medial prefrontal cortex |
| NAAG | N-acetylaspartylglutamate |
| NMDA | N-methyl-D-aspartate |
| NTS | nucleus tractus solitarius |
| PAG | periaqueductal gray |
| PL | pre-limbic |
| PLC | phospholipase C |
| RVM | rostral ventromedial medulla |
| TRPV1 | transient receptor potential vanilloid 1 |

## 2.1 Introduction

As the most abundant excitatory neurotransmitter in the central nervous system (CNS), glutamate plays a pivotal role in main physiological brain functions. Glutamate exerts its effects through the activation of ligand-gated ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). iGluRs are ion channel receptors, divided into N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainate (KA) receptors, which mediate fast responses, associated with long-lasting modifications in synaptic transmission (Bleakman and Lodge 1998; Yamakura and Shimoji 1999), while mGluRs are G-protein-coupled receptors (GPCRs) subdivided into three groups (mGluR1–mGluR8) based on sequence homology, intracellular pathways, and pharmacological profile. Group I mGluRs, consisting of $mGluR_1$ and $mGluR_5$, are postsynaptically located and positively coupled to phospholipase C, and their activation leads to the intracellular calcium mobilization. Group II mGluRs, consisting of mGluR2 and mGluR3, and group III mGluRs, consisting of mGluR4, mGluR6, mGluR7, and mGluR8, are mainly presynaptic and coupled to the inhibition of adenylyl cyclase activity and to other signaling pathway, including the activation of mitogen-activated protein kinase cascade (Tian et al. 2010). mGluRs, by modulating ion channel activity and neurotransmitter release, play a modulatory role on

CNS synaptic excitability (Maione et al. 1998a; Cartmell and Schoepp 2000). Thus, signaling via these receptors is slower and longer-lasting driving to a fine-tuning of glutamate transmission.

Hyperexcitability of glutamatergic system is the main event occurring in central sensitization associated to chronic pain. Apart from classical symptoms, such as allodynia (pain experience following a not-painful stimulus) and hyperalgesia (increased pain perception from a painful stimulus), chronic pain presents comorbidity with affective and cognitive impairments. mGluRs are suitable pharmacological substrate for producing a fine modulation of glutamate transmission, whose hyperactivity or altered functioning is often associated with neurodegenerative, neurological, and psychiatric diseases. The effects of mGluRs stimulation in supraspinal areas of the pain pathway are summarized in Fig. 2.1. By this subject, mGluRs

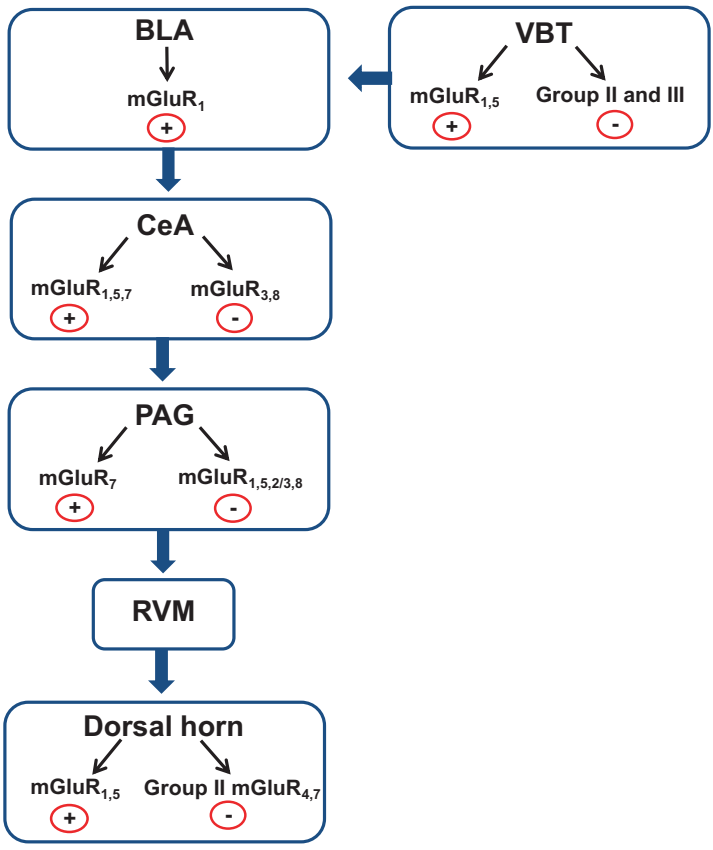


**Fig. 2.1** Scheme indicating the effect of mGluRs in supraspinal areas of the pain pathway. **+** indicates a facilitatory effect on pain transmission, while **−** indicates an inhibitory effect on pain transmission. *VBT* ventrobasal thalamus

pharmacological manipulation may represent an optimal strategy to treat chronic pain, including untreatable forms such as neuropathic pain, and associated affective and cognitive impairments.

## 2.2 mGluRs and Pain Processing

Increasing evidence supports a crucial role of mGluRs in nociceptive transmission, given their extensive expression all along the nociceptive neuroaxis, such as the peripheral sensory terminals, dorsal root ganglia, spinal cord dorsal horn, rostral ventromedial medulla (RVM), periaqueductal gray (PAG), thalamus, amygdala, and cortex. The large variety and different synaptic distribution of mGluR subtypes determine their diverse role in pain transmission. Group I mGluRs are mainly expressed in the postsynaptic membrane, whereas group II and III mGluRs are localized presynaptically where they serve as auto- or hetero-receptors (Ohishi et al. 1995). Generally, stimulation of group I mGlu receptors facilitates pain (Hama 2003; Chiechio and Nicoletti 2012; Palazzo et al. 2014a, b). Conversely, activation of presynaptic mGluRs on glutamatergic terminals leads to a decrease in glutamate release (Attwell et al. 1995; Battaglia et al. 1997) correcting hyperactivity of glutamatergic system associated with chronic pain (Gerber et al. 2000). Within the pain descending pathway, high glutamate levels are associated with antinociception throughout a facilitation of the descending pain system functioning (Behbehani and Field 1979). In fact, the activation of group I or groups II and III mGluRs exerts antinociceptive or pronociceptive opposite effects (Marabese et al. 2005, 2007a, b) depending on the mGluR subtype signaling and its location on glutamatergic or GABAergic terminals.

Over the last decade, accumulating evidence has strengthened the evidence that dysfunction of the glutamate system is linked with the pathophysiological mechanisms responsible for chronic pain development (Neugebauer 2001). Neuropathic or inflammatory injury triggers structural and functional changes in the peripheral or central sensory circuits, resulting in altered nociceptive signal processes, such as spontaneous pain, allodynia, and hyperalgesia (Neugebauer et al. 2009; Goudet et al. 2008; Byrnes et al. 2009). Under neuropathic pain conditions, enhanced glutamate release and overactivation of glutamate receptors have been observed in cortical areas involved in pain-related responses, including the anterior cingulate (ACC), insular, and prelimbic-infralimbic (PL-IL) cortex (Giordano et al. 2012; Hung et al. 2014). Furthermore, chronic pain interferes with specific limbic brain areas affecting neuropsychological processes which are glutamate-dependent, such as cognition, memory, and decision-making. mGluRs are supraspinally expressed within limbic system thus controlling negative affective disorders associated with chronic pain (Ferraguti and Shigemoto 2006; Latremoliere and Woolf 2009).

## 2.3 Group I mGluRs

The difficulty to develop selective agonists or antagonists for specific mGluR subtype arises from the sequence homology of mGluRs within the ligand binding site, which presents a hydrophilic moiety which makes the compound too hydrophilic to penetrate the blood-brain barrier for brain exposure. The identification, in the last years, of novel compounds acting as PAMs or NAMs, has guaranteed selectivity and lipophilicity since allosteric binding sites proved less conserved among the other mGluRs and do not require hydrophilic molecules. Activation of group I mGluRs generally facilitates nociception (Bhave et al. 2001) and mediates the development of inflammatory hyperalgesia (Walker et al. 2000; Palazzo et al. 2004). The role of supraspinal group I mGluRs in controlling pain responses has been investigated in the ventrobasal thalamus, periaqueductal gray, rostral ventromedial medulla, and amygdala.

*Thalamus* Ventrobasal thalamus is a crucial relay point processing the somatosensory information which from the spinal cord reach the cerebral cortex. At this level, mGluR1, mGluR5, and NMDA receptor stimulation enhances neuronal responses to nociceptive stimuli. Conversely, NMDA receptor, mGluR1, or mGluR5 blockade reduced the neuronal responses (Salt and Binns 2000).

*Amygdala and Cortex* Basolateral (BLA) and central nucleus (CeA) of the amygdala are deeply involved in the emotional consequences of pain, such as pain-related anxiety and depression-like behaviors. While the electrical manipulation of CeA activity does not modify the spontaneous nociceptive behaviors (Carrasquillo and Gereau 2008; Veinate et al. 2013), chronic pain leads to increased synaptic transmission in the CeA, associated with the induction or maintenance of hypersensitivity observed in different pain models.

The activation of group I mGluRs in the amygdala is generally associated with pronociceptive effects (Neugebauer et al. 2003a, b; Kolber et al. 2010). Conversely, the blockade of mGluR1 inhibits pain stimuli-induced audible and ultrasonic vocalizations (Han and Neugebauer 2005) and decreases excitatory postsynaptic currents in neurons within the CeA in arthritic rats (Neugebauer et al. 2003a; Ren and Neugebauer 2010). It has been recently shown that group I mGluRs are involved in the plastic changes that develop in the BLA and medial prefrontal cortex (mPFC) circuitry in chronic pain states (Ji and Neugebauer 2011; Guida et al. 2015). Later on, Luongo et al. (2013) have showed that intra-BLA microinjection of (S)-3,5-dihydroxyphenylglycine (DHPG), a group I mGluR agonist, reverted neuronal phenotypical changes occurring in the mPFC, under chronic pain condition. The 7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxylate ethyl ester, CPCOOEt, a selective mGluR1 antagonist, but not 2-methyl-6-(phenylethynyl)-pyridine, MPEP, a selective mGluR5 antagonist, prevented alteration in mPFC under chronic pain condition, suggesting that mGluR1, but not mGluR5, plays a role in the modulation of BLA-mPFC circuitry, which is thought to be a key substrate for affective/cognitive impairments associated with chronic pain.