European Journal of Pharmacology 639 (2010) 115–122

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Group II metabotropic glutamate receptors ($mGlu_{2/3}$) in drug addiction

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ARTICLE INFO

Article history:
Accepted 20 January 2010
Available online 2 April 2010

Keywords:
Addiction
Glutamate
Group II metabotropic glutamate receptor
($mGlu_{2/3}$ receptor)
LY379268
LY341495

ABSTRACT

Drug addiction is characterized by maladaptive decision-making and dysfunctional brain circuitry regulating motivated behaviors, resulting in loss of the behavioral flexibility needed to abstain from drug seeking. Hence, addicts face high risk of relapse even after prolonged periods of abstinence from drug use. This is thought to result from long-lasting drug-induced neuroadaptations of glutamate and dopaminergic transmission in the mesocorticolimbic and cortico-striatal circuits where group II metabotropic glutamate receptors ($mGlu_{2/3}$ receptors) are densely expressed. $mGlu_{2/3}$ receptors presynaptically control glutamate as well as dopamine release throughout the mesocorticolimbic structures involved in reward processing and drug seeking, and their function is reduced after prolonged exposure to drugs of abuse. In pre-clinical models, $mGlu_{2/3}$ receptors have been shown to regulate both reward processing and drug seeking, in part through the capacity to control release of dopamine and glutamate respectively. Specifically, $mGlu_{2/3}$ receptor agonists administered systemically or locally into certain brain structures reduce the rewarding value of commonly abused drugs and inhibit the reinstatement of drug seeking. Given the ability of $mGlu_{2/3}$ receptor agonists to compensate for and possibly reverse drug-induced neuroadaptations in mesocorticolimbic circuitry, this class of receptors emerges as a new therapeutic target for reducing relapse in drug addiction.

Contents

1. Addiction as a cognitive disorder

Drug addiction is often described as a cognitive disorder that is characterized by maladaptive decision-making and dysfunctional motivational circuits (Kalivas and Volkow, 2005; Koob and Le Moal, 2001; Schoenbaum et al., 2006). Addicts lose interest in obtaining natural reward and choose to seek drugs of abuse despite their insights into the adverse outcomes of their decision. Thus, addicts lack the necessary behavioral flexibility required to implement their stated desire to abstain from drug seeking. Instead, they engage in repeated drug seeking and exhibit increased vulnerability to relapse even after prolonged periods of withdrawal (Kalivas and O'Brien, 2008). This is thought to result from long-lasting neuroadaptations in the brain circuitry regulating motivated behaviors caused by repeated exposure to drugs of abuse (Graybiel, 2008; Kalivas and Volkow, 2005). Emerging research studies over the past few years illustrate the role of glutamate neurotransmission in the neurobiology of addiction

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doi:10.1016/j.ejphar.2010.01.030

(Kalivas, 2009). In particular, this review will describe the physiology and drug-induced pathologies in group II metabotropic glutamate receptors ($mGlu_{2/3}$ receptors) supporting therapeutic interventions targeting this receptor class in treating drug addiction.

2. Neurocircuitry of motivated behavior and relapse

It is well established that increased vulnerability to relapse after chronic exposure to drugs of abuse is rooted in the long term neuroadaptations in the neural circuitry of normal goal oriented behavior (Kalivas and Volkow, 2005). The prefrontal cortex (PFC) glutamatergic projection to the ventral striatum (nucleus accumbens; NAc) is a key component of the circuit involved in initiating and learning adaptive behaviors (Graybiel, 2008; Hyman et al., 2006), and this projection is in turn regulated by mesocorticolimbic dopaminergic projections from the ventral tegmental area (VTA), signaling the salience and facilitating learning of the relevant experience (Redgrave and Gurney, 2006; Schultz and Dickinson, 2000). Projections into PFC and NAc from other brain areas like hippocampus and basolateral amygdala are thought to provide previously learned, relevant contextual and emotional information associated with the experience at hand (Bast et al., 2001; Phelps and LeDoux, 2005; Rudy and Matus-Amat, 2005; Swanson and Petrovich, 1998). As well, other areas like the extended amygdala (bed Nucleus of stria terminalis, central amygdala, and NAc shell) sending projections into PFC/NAc convey signals about the organism's internal state that contribute to ongoing information processing (Kelly and Strick, 2004; Reynolds and Zahm, 2005; Swanson and Petrovich, 1998). Importantly, in addition to regulating adaptive behavioral responses, the PFC-NAc glutamatergic pathway is involved in addiction related behaviors, and is necessary and sufficient for reinstating drug seeking behavior in some animal models of relapse (Fig. 1) (Kalivas and Volkow, 2005).

Lesion or inactivation of the prelimbic PFC or NAc prevents reinstatement of drug seeking in extinguished animals, while stimulation of either promotes drug seeking in the absence of a drug- or cue-prime (Capriles et al., 2003; Cornish et al., 1999; Cornish and Kalivas, 2000; Di Ciano and Everitt, 2001; McFarland et al., 2004; McFarland and Kalivas, 2001; McFarland et al., 2003; McLaughlin and See, 2003; Peters et al., 2008). Moreover, behavioral electrophysiological data indicate an increase in firing rate of PFC pyramidal neurons (Sun and Rebec, 2006), as well as subpopulations of NAc medium spiny neurons (MSN) (Carelli and Ijames, 2000) during reinstatement of cocaine seeking. Human imaging studies have also identified correlations between craving and increased activity in the ventral orbital cortex, cingulate cortex, and ventral striatum upon drug or cue exposure (Breiter et al., 1997; Breiter and Rosen, 1999; Kufahl et al., 2005; Risinger et al., 2005; Wilson et al., 2004).

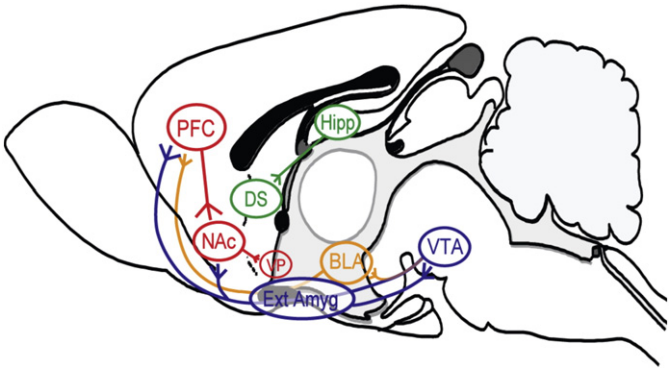

Fig. 1. The neurocircuitry of relapse. Drug, cue, and stress induced relapse after cocaine self-administration require the projections from prefrontal cortex (PFC) to nucleus accumbens (NAc) to ventral pallidum (VP) (red pathway), commonly referred to as the final common pathway. In addition, cue induced relapse depends on basolateral amygdala (BLA) projections to PFC, and stress induced relapse requires activation of the extended amygdala (Ext Amyg)—ventral tegmental area (VTA) pathway, which in turn feeds into PFC and NAc. PFC is not involved in context induced relapse after abstinence; instead, projections from hippocampus (Hipp) to dorsal striatum (DS) (Fuchs et al., 2005, 2006) and NAc shell are thought to be involved (Bossert et al., 2005b).

In addition, other brain regions are compulsory depending on the stimulus used to elicit drug seeking (Fig. 1). For example, cue primed relapse requires basolateral amygdala while stress induced relapse requires the extended amygdala (McFarland et al., 2004; See, 2002; Shaham et al., 2000). Corresponding to the discovery of this circuitry, many laboratories have focused on identifying and reversing enduring neuroadaptations in the relapse circuitry encompassing protein biochemistry, gene expression, spine morphology, and electrophysiology (Hyman et al., 2006; Kalivas, 2009; Kauer and Malenka, 2007). Different animal models are used to examine aspects of drug reward, including intracranial self-stimulation, conditioned place preference, or self-administration of the relevant substance, while other models are thought to reflect enduring brain changes associated with increased reinforcing value and/or vulnerability to relapse, including locomotor sensitization and reinstatement of drug seeking (Epstein et al., 2006; Sanchis-Segura and Spanagel, 2006). Using these animal models, $mGlu_{2/3}$ receptors have emerged as an important substrate for drug-induced neuroadaptations and one that may have utility in regulating drug seeking and other addiction related behaviors.

3. $mGlu_{2/3}$ receptors and regulation of neurotransmitter release

Group II metabotropic receptor ($mGlu_{2/3}$ receptors) family includes 2 subtypes both coupled to Gi proteins; mGlu2 receptors are expressed outside the active zone on presynaptic axon terminals to negatively regulate neurotransmitter release, while mGlu3 receptors are localized pre- and post-synaptically as well as on glia with a less clear overall function, but including negative regulation of transmitter release (Ohishi et al., 1993b; Richards et al., 2005; Schoepp, 2001; Tamaru et al., 2001; Testa et al., 1998). $mGlu_{2/3}$ receptors can be homosynaptic, regulating glutamate release, or heterosynaptic regulating release of dopamine and γ-aminobutyric acid (GABA) (Hu et al., 1999; Karasawa et al., 2006; Schoepp, 2001; Xi et al., 2009). Gi coupling of $mGlu_{2/3}$ receptors controls release through different mechanisms including activation of presynaptic K+ channels, inhibition of presynaptic Ca2+ channels, or direct interference with vesicular release (Anwyl, 1999).

In the PFC, $mGlu_{2/3}$ receptors appear to be tonically activated by endogenous glutamate. Microdialysis studies reveal an increase in PFC glutamate levels upon infusion of a selective $mGlu_{2/3}$ receptor antagonist (LY341495) (Melendez et al., 2005; Xie and Steketee, 2008). However, perfusion of a selective agonist ((2R,4R)-4-aminopyrrolidine-2,4-dycarboxylate (APDC)) was without effect, suggesting the presence of ceiling-like glutamatergic tone on $mGlu_{2/3}$ receptors (Melendez et al., 2005). In addition, infusion of the antagonist LY341495 in the prefrontal cortex increased glutamate levels in subcortical regions of the reward circuitry including the nucleus accumbens and ventral tegmental area (Xie and Steketee, 2008). This is possibly due to reduced inhibition resulting in facilitated excitatory output from the PFC.

In the nucleus accumbens, data support the presence of endogenous glutamatergic tone on $mGlu_{2/3}$ receptors regulating both glutamate and dopamine levels. Electrophysiological recordings from NAc slices reveal presynaptic autoregulation of glutamate release by $mGlu_{2/3}$ receptors. Bath application of the selective agonists (S)-4-carboxy-3-hydroxyphenylglycine ((1 S,3 S)-ACPD) and (2 S,1′S,2′S)-2-(2′-carboxycyclopropyl)glycine (L-CCG1) increased paired pulse ratios and reduced miniature excitatory post synaptic currents (mEPSC) frequency without affecting their amplitude, pointing to a presynaptic mode of action (Manzoni et al.,