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Group III metabotropic glutamate receptors and drug addiction

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Abstract

Neuroadaptations of glutamatergic transmission in the limbic reward circuitry are linked to persistent drug addiction. Accumulating data have demonstrated roles of ionotropic glutamate receptors and group I and II metabotropic glutamate receptors (mGluRs) in this event. Emerging evidence also identifies G α i/o-coupled group III mGluRs (mGluR4/7/8 subtypes enriched in the limbic system) as direct substrates of drugs of abuse and active regulators of drug action. Auto- and heteroreceptors of mGluR4/7/8 reside predominantly on nerve terminals of glutamatergic corticostriatal and GABAergic striatopallidal pathways, respectively. These presynaptic receptors regulate basal and/or phasic release of respective transmitters to maintain basal ganglia homeostasis. In response to operant administration of common addictive drugs, such as psychostimulants (cocaine and amphetamine), alcohol and opiates, limbic group III mGluRs undergo drastic adaptations to contribute to the enduring remodeling of excitatory synapses and to usually suppress drug seeking behavior. As a result, a loss-of-function mutation (knockout) of individual group III receptor subtypes often promotes drug seeking. This review summarizes the data from recent studies on three group III receptor subtypes (mGluR4/7/8) expressed in the basal ganglia and analyzes their roles in the regulation of dopamine and glutamate signaling in the striatum and their participation in the addictive properties of three major classes of drugs (psychostimulants, alcohol, and opiates).

Keywords

group III metabotropic glutamate receptors; cocaine; amphetamine; alcohol; opiate

Introduction

L-glutamate (glutamate) is a major neurotransmitter in the mammalian brain. This transmitter interacts with both ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs) to mediate or regulate a variety of cellular activities and synaptic transmission [1]. The mGluRs belong to the G protein-coupled receptor family. Through various G proteins, they connect to multiple intracellular second messenger systems. Based on the connection specificity, eight mGluR subtypes (mGluR1-8) so far cloned are classified into three functional groups [2]. Group I mGluRs (mGluR1 and 5 subtypes) are coupled to G α q proteins, through which mGluR1/5 signals activate phospholipase C β 1. This activation increases phosphoinositol hydrolysis, resulting in

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Compliance with ethics guidelines

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intracellular Ca^{2+} release and protein kinase C (PKC) activation [2]. Both group II (mGluR2/3) and group III (mGluR4/6/7/8) receptors are coupled to G α i/o proteins. Activation of them inhibits adenylyl cyclase and cAMP formation, thereby limiting downstream protein kinase A (PKA) activation. Since mGluRs function through their downstream signaling pathways, they usually modulate relatively slow cellular responses as opposed to iGluRs that usually mediate fast synaptic transmission in the central nervous system.

Drug addiction is a persistent cognitive disorder that is characterized by compulsive drug craving, seeking, and ingestion in spite of severe adverse consequences [3,4]. The potential brain mechanisms underlying this disorder remain elusive. Available data support a notion that long-lasting neuroadaptations in the limbic reward circuitry induced by repeated exposure of drugs of abuse mediate addictive behavior [4,5]. The ventral tegmental area (VTA) is a key component of the reward circuitry. The VTA dopaminergic neurons project to the ventral striatum/nucleus accumbens (NAc) and the prefrontal cortex (PFC). The latter together with other limbic structures such as the hippocampus and amygdala send glutamatergic projections to the NAc. These limbic areas are the main central substrates of drugs and are actively involved in drug action [4]. In addition, the dorsal striatum/caudate putamen (CPU) receives dopaminergic and glutamatergic inputs from the substantia nigra (SN) and the cortex, respectively, and contributes to learning and memory and compulsive disorders [5].

Enriched glutamatergic innervation and dense pre- and postsynaptic glutamate receptor distribution in basal ganglia reward structures situate glutamate well as an equally important regulator as dopamine in drug addiction. As supported by accumulated data [6,7], basal ganglia glutamatergic components are sensitive to addictive drugs, such as psychostimulants (cocaine and amphetamine), alcohol, and opiates. In response to repeated exposure of drugs, glutamatergic transmission undergoes enduring remodeling and adaptations, leading to addictive behavior. Indeed, iGluRs have been extensively investigated, and their adaptations and contributions to drug action have been reviewed previously [8–10]. Group I and II mGluRs are also important for drug addiction, as reviewed elsewhere [11–15]. In addition to group I/II mGluRs, group III mGluRs are expressed in the mesolimbic reward system. While investigation of group III mGluRs seems to be still trailing behind group I/II receptors, available data support their emerging roles in drug action. In this review, we will summarize progress from the studies concerning group III mGluRs. We will mainly review three group III mGluR subtypes (4/7/8) as they are enriched in the reward circuitry related to drug addiction, while another group III subtype (mGluR6) is expressed only in the retina (see below). Of note, the importance of group III mGluRs is not limited to addiction. Malfunctional group III mGluRs have been linked to the pathogenesis of many other neurological diseases, such as schizophrenia [16], anxiety [16,17], and Parkinson's disease [17,18].

Localization and function of group III mGluRs in the reward circuitry

Like other brain regions, localization of group III mGluRs in the basal ganglia is predominantly presynaptic [19] (Fig. 1). Both mGluR4 and 7 presynaptic autoreceptors are seen on the glutamatergic corticostriatal terminals [18,19]. They are also found on nerve terminals of GABAergic striatopallidal and striatonigral pathways and serve as presynaptic heteroreceptors [20–22]. mGluR8 mRNAs are expressed in the cortex and striatum [23]. A possibility is thus that these receptors could presynaptically reside on corticostriatal and/or striatonigral/striatopallidal terminals. mGluR6 is restrictedly expressed in the retina, but not in the basal ganglia [24]. As such, mGluR6 is reasoned to play an insignificant role in drug addiction. Compared to the dominant presynaptic distribution, the postsynaptic distribution

of group III mGluRs in the basal ganglia is less clear [18] and is limited to some postsynaptic mGluR7 in striatal neurons [21]. Thus, focus at present remains on the presynaptic site when localization and function of group III mGluRs are investigated.

Electrophysiological experiments with available pharmacological agents selective at either the group or the subtype level have provided evidence for potential functional roles of these receptors in different reward pathways. In the corticostriatal pathway, group III receptor agonists, L-serine-O-phosphate (L-SOP) and L-2-amino-4-phosphonobutyrate (L-AP4), suppressed synaptic responses to cortical stimulation in postsynaptic striatal neurons [25–27]. This may result from the inhibition of glutamate release from corticostriatal terminals, likely through presynaptic mGluR4 [27]. The mGluR8 agonist (*S*)-3,4-dicarboxyphenylglycine [(*S*)-DCPG] did not produce the same effect as the above agonists [27]. Thus, the mGluR8's function in regulating corticostriatal synapses, if mGluR8 is present on presynaptic terminals, remains elusive. Group III receptors also inhibit the GABAergic striatopallidal pathway. L-AP4 depressed striatal-evoked synaptic responses, inhibitory postsynaptic currents (IPSCs), in the globus pallidus [28,29]. This effect may be due to the inhibition of GABA release from striatopallidal terminals [30], and mGluR4 activation seems to be crucial [29,31]. At GABAergic striatonigral synapses, L-AP4 inhibited striatal-evoked IPSCs in the substantia nigra [32]. Thus, at either glutamatergic or GABAergic synaptic sites surveyed so far in the basal ganglia reward circuitry, group III mGluRs (one or more subtypes) consistently act to inhibit synaptic transmission via a presynaptic mechanism.

Psychostimulants

An early study noted the impact of group III receptor agents on behavioral responses to acute cocaine [33]. In chronically cannulated and conscious rats, microinjection of the group III receptor agonist L-AP4 or antagonist MPPG into the CPu did not alter basal motor activity [33], although L-AP4 injected into the NAc induced relatively modest motor stimulation [34]. Of note, L-AP4 injected into the CPu reduced hyperlocomotion induced by acute cocaine or amphetamine, and MPPG reversed this effect [33]. Similarly, L-AP4 activation of MPPG-sensitive group III receptors in the rat NAc attenuated locomotor responses to amphetamine [35]. Systemic administration of a new group III agonist, (1*S*,3*R*,4*S*)-1-aminocyclopentane-1,3,4-tricarboxylic acid (ACPT-I), reduced the behavioral effect of amphetamine [36]. Thus, group III mGluRs in both the dorsal and ventral striatum regulate behavioral responsiveness to psychostimulants. And an enhanced receptor activity usually functions to lower behavioral sensitivity to stimulants. How group III receptors and which subtype of them regulate motor sensitivity to stimulants is unclear. The presynaptic regulation of local transmitter release by these receptors may cast light. L-AP4 has been found to reduce extracellular dopamine levels in the CPu and NAc, whereas MPPG enhanced dopamine in these regions [37,38]. More importantly, L-AP4 attenuated amphetamine-stimulated dopamine release in the CPu [38]. Thus, by inhibiting dopamine release, group III receptors may inhibit motor responses to stimulants. The receptor can directly inhibit dopamine release through the group III heteroreceptor on dopaminergic terminals if their presence on the terminal can be proven. Alternatively, the receptor can indirectly regulate dopamine release via glutamate. Striatal glutamate has long been recognized to facilitate dopamine release [39]. Inhibition of glutamate release by group III autoreceptors may result in parallel depression of dopamine release. At present, whether group III receptors directly modulate the phasic glutamate release in the striatum induced by stimulants remains to be an interesting topic, while L-AP4 and the group III receptor antagonist (R, *S*)- α -methylserine-O-phosphate (MSOP) decreased and increased the baseline extracellular level of glutamate in the rat NAc, respectively [40]. In addition to the regulation of transmitter release by an auto- or heteroreceptor mechanism, mGluR7a shows

the presence at postsynaptic sites in both striatonigral and striatopallidal medium spiny output neurons [21]. L-AP4 in fact showed inhibition of evoked synaptic responses in the NAc at least partially via a postsynaptic mechanism [41]. Thus, postsynaptic inhibition of striatal cellular responses to stimulants is possible. This postsynaptic mechanism, if there is, is likely to cooperate with the presynaptic modulation to dynamically control synaptic and motor responses to drugs.

Neuroadaptations of group III mGluRs may occur in response to chronic stimulant exposure and may accordingly regulate the long-term effect of drugs. Like other glutamate receptors, group III mGluRs are sensitive targets of stimulants. While acute cocaine reduced mGluR8 protein expression in the rat striatum [42], chronic amphetamine induced a profound increase in mGluR8 mRNAs in the rat striatum and especially cerebral cortex [43]. A long-lasting nature of this increase, as it remained 21 days after drug withdrawal, is noticeable. It is appreciated that altered gene expression, if lasted long enough, could be a critical transcription-dependent adaptation contributing to the enduring receptor plasticity and drug addiction. Thus, the increased mGluR8 mRNA expression, if it can be translated to a parallel increase in protein expression and function, may reflect an important element in the remodeling of excitatory synapses related to behavioral plasticity. In addition, a robust increase in cortical mGluR8 may lead to an increased number of mGluR8 autoreceptors on corticostriatal terminals. This enhances mGluR8 tone on glutamate release from this pathway and allows mGluR8 to participate in the reshaping of excitatory synapses. In the central amygdala, loss of group III mGluR function was revealed in rats after chronic cocaine exposure [44].

Operant drug self-administration paradigm provides a robust animal model for mimicking core features of addiction in humans. Increasing evidence from studies using this model shows the reliable participation of iGluRs and group I/II mGluRs in drug seeking behavior [8–15]. Recently, investigators have started to pay attention to group III mGluRs and have utilized this model to define the role of these receptors in drug consumption. Systemic administration of the mGluR7 selective allosteric agonist N,N'-dibenzylhydrazyl-ethane-1,2-diamine dihydrochloride (AMN082) inhibited cocaine self-administration [45]. AMN082 had no impact on sucrose self-administration, indicating the specific inhibition of cocaine reward by this agent. Microinjection of AMN082 into the NAc, although not the CPu, was effective as systemic administration [45]. An mGluR7 selective allosteric antagonist 6-(4-methoxyphenyl)-5-methyl-3-pyridin-4-ylisoxazolo [4,5-c]pyridine-4(5H)-one (MMPiP) blocked the AMN082 effect. Similar to the self-administration model, AMN082 inhibited cocaine-induced enhancement of electrical brain-stimulation reward [45] and reinstatement of cocaine-seeking in a rat relapse model [46]. These data support the role of mGluR7 in cocaine seeking. Of note, AMN082, unlike L-AP4, selectively alters extracellular levels of GABA and glutamate, but not dopamine [47]. This suggests that AMN082 may target a pathway downstream to NAc dopamine (i.e., the NAc-ventral pallidum GABAergic pathway) to exert its anti-cocaine effect. In support of this, local injection of AMN082 into the ventral pallidum inhibited cocaine self-administration [47].

Alcohol

As for other drugs of abuse, alcohol induces changes in the limbic reward system. These experience-dependent neuroadaptations contribute at least in part to alcohol dependence (alcoholism). Among adaptations at multiple levels, plastic changes in glutamatergic transmission play a central role [48]. Regarding group III mGluRs, several recent studies unravel their importance in glutamate receptor plasticity and alcohol seeking. Current attention seems to focus on mGluR7, probably due to (1) its relatively higher concentration in the basal ganglia compared to other group III subtypes, (2) its highest evolutionary

conservation among all mGluRs suggesting significant physiological roles [49], and (3) its genetic linkage to heritable ethanol drinking [50]. In the first study linking mGluR7 to alcohol seeking behavior, Vadasz *et al.* identified mGluR7 as a cis-regulated gene for alcohol consumption, and mice carrying mutations that lead to lower mGluR7 transcript expression consumed more alcohol than controls [50]. In a recent study, the mGluR7 allosteric agonist AMN082 reduced rat ethanol consumption and preference without affecting taste preference [51], although the other study in mice found that AMN082 reduced both ethanol and sucrose administration [52]. AMN082 also reduced the reinstatement of ethanol-induced conditioned place preference [53]. In contrast to AMN082, the mGluR7 selective antagonist MMPIP enhanced ethanol intake and reversed the effect of AMN082 [51,53]. In mGluR7 knockout mice, alcohol consumption was increased relative to wild-type mice [54]. Viral-mediated mGluR7 knockdown in the NAc induced excessive alcohol drinking and augmented ethanol-induced conditioned place preference [55]. Apparently, mGluR7 possesses the ability to suppress alcohol drinking as seen in the case of cocaine. Loss of mGluR7 activity contributes to plastic changes in glutamatergic transmission, leading to drug seeking behavior.

Other group III receptor subtypes have also been studied for their implications in alcohol effects. Mice lacking mGluR4 showed a higher motor response to novelty than did wild-type mice [56]. However, these mutant mice did not show the stimulatory motor activity in response to a behaviorally active dose of ethanol. There were no differences between mutant and wild-type strains in ethanol consumption or preference, severity of ethanol-induced acute withdrawal, or duration of loss of righting reflex. Thus, mGluR4 is involved in mediating ethanol-induced motor stimulation, although the receptor seems to lack the association with ethanol consumption. The mGluR8 selective agonist (*S*)-3,4-dicarboxyphenylglycine [(*S*)-3,4-DCPG], when administered systemically, attenuated rat alcohol self-administration (reinforcing effect of alcohol) and cue-induced reinstatement of alcohol seeking [57]. This suggests the inhibitory modulation of the addictive properties of alcohol by mGluR8. However, (*S*)-3,4-DCPG also decreased spontaneous locomotor activity [57]. Therefore, an mGluR8 agent with less motor-suppressant side effects is preferred to clarify the distinct modulation of mGluR8 on alcohol seeking behavior.

Opiates

While glutamate is important for opiate dependence, only a few reports have described potential anti-addictive activity of group III mGluRs toward opiates so far. Intracerebroventricular injections of the group III receptor antagonist α -methyl-L-amino-4-phosphonobutanoate (MAP4) decreased the time spent in morphine withdrawal in rats [58]. However, MAP4 is known to activate group II mGluRs [58]. Thus, a further investigation using a group III receptor selective agonist ACPT-I was carried out in mice to define the specific role of group III mGluRs [59]. Peripheral administration of this agonist attenuated all morphine withdrawal symptoms, including vertical jumping, wet dog shake, paw shake, body tremor, and body weight loss [59]. Mechanisms underlying the effect of ACPT-I are unclear. The presynaptic regulation of transmitter release may again play a role. An increase in glutamate release has been seen during morphine withdrawal [60,61], which is believed to link to withdrawal symptoms. Thus, ACPT-I may stimulate presynaptic group III receptors to inhibit glutamate release, thereby attenuating the symptoms. In addition, the probability of GABA release in the VTA was increased during withdrawal from chronic morphine due to the upregulated cAMP-dependent signaling [62]. This could be one adaptive mechanism underlying morphine withdrawal symptoms. ACPT-I may therefore activate group III mGluR heteroreceptors to inhibit GABA release and attenuate withdrawal symptoms.

Conclusions

Glutamatergic transmission in the basal ganglia has now been appreciated to be critical for drug addiction. Early studies have established iGluRs and mGluRs (mainly group I/II) as direct substrates of drugs and active regulators of drug effects. In response to drug exposure, these receptors in striatal and cortical neurons show marked and dynamic changes in expression, trafficking/redistribution, and function. For group III mGluRs, even though limited studies have been attempted at present, emerging evidence ties them to the remodeling of excitatory synapses and persistent drug seeking. The high level of expression of mGluR7 in the limbic reward circuitry implies its roles in drug action. In fact, evidence associates this receptor with addictive effects of psychostimulants, alcohol, and opiates. In addition to mGluR7, mGluR4 and mGluR8 are important for drug action. Due to a predominant presynaptic distribution pattern, group III mGluRs are believed to exert their roles via a presynaptic mechanism, although a postsynaptic modulation to a certain extent cannot be ruled out. It is anticipated that studies on group III receptor in the addiction research field will grow rapidly. The advancement of developing (1) pharmacological agents with higher subtype selectivity and (2) conditional knockout mouse lines will facilitate these studies. All future research efforts will ultimately inform group III mGluRs as to their clinical relevance, and assist in our understanding the pathogenesis of psychiatric illnesses and in developing therapeutic agents for drug addiction.

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Fig. 1.

A schematic diagram illustrating distribution of group III mGluRs in the basal ganglia. The striatum (CPu and NAc) receives dopaminergic inputs from the substantia nigra pars compacta (SNc) and VTA and glutamatergic (Glu) inputs from the cerebral cortex, thalamus, and other forebrain areas (i.e., glutamatergic inputs from the hippocampus and amygdala to the NAc). Striatal neurons project two GABAergic pathways (D1 receptor-mediated direct and D2 receptor-mediated indirect pathways) to regulate outflow of the basal ganglia to the motor cortex. Group III mGluRs (mGluR4, mGluR7, and/or mGluR8) are distributed primarily in presynaptic terminals. Other abbreviations: GPe, external globus

pallidus; GPi, internal globus pallidus; VP, ventral pallidum; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus.