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Addiction Research

The Role of Metabotropic Glutamate Receptor Subtype 5 in Mouse Models of Cocaine Addiction

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ABSTRACT

Cocaine is a psychostimulant that is one of the most widely used illicit drugs, particularly in America. Cocaine addiction is a chronic relapsing disease that is characterized by drug craving and loss of inhibitory control. Animal models of psychiatric diseases are essential to identify underlying neural circuitry and to test the effectiveness of novel pharmacotherapies to prevent relapse. Current research using animal models indicates that type 5 metabotropic glutamate receptors may be of particular importance to the onset and maintenance of cocaine addiction. This literature review provides a general overview of the glutamate system, and the animal models frequently used in the study of addiction and summarizes peer-reviewed research focused on cocaine-induced adaptations to the type 5 metabotropic glutamate receptors in mice. Cocaine administration in mouse models induces a range of neural changes in the brain, reflecting the neuroadaptations associated with cocaine addiction. Cocaine-induced adaptations to type 5 metabotropic glutamate receptor vary by brain region and by methodological constraints. Key neural changes that occur in the mouse brain following cocaine administration include adaptations in the dopaminergic and glutamatergic systems. The interplay between mGluR5 and the dopamine system plays a significant role in the neurobiological adaptations that drive cocaine addiction. Lastly, we cover the potential efficacy of targeting this receptor as a novel therapeutic option to prevent cocaine relapse. Selective antagonists of this receptor have been studied for their potential therapeutic effects in mouse models of cocaine addiction. These compounds reduce the conditioned responses to drug-associated cues and reduce the motivation to seek cocaine, thereby inhibiting relapse-like behavior, and have been found to modulate synaptic plasticity in brain regions involved in addiction, such as the nucleus accumbens and prefrontal cortex. Overall, these compounds demonstrate promising effects in mouse models of cocaine addiction.

Keywords

Addiction, Animal model, Cocaine, mGluR5, Mice.

Introduction

Cocaine is a psychostimulant that is one of the most widely used illicit drugs, particularly in America. Cocaine addiction is a chronic relapsing disease that is characterized by drug craving and loss of inhibitory control [1]. In 2021, 4.8 million people 12 years or older used cocaine, and 1.4 million people were classified as having cocaine use disorder [2]. Cocaine abuse is linked to significant health concerns for the individual, including various cardiovascular problems, mental health disorders, and cognitive impairment [3-5]. Cocaine abuse also has a strong negative impact on family and work relationships. From a wider perspective, cocaine abuse is a significant public health concern, affecting the transmission of infectious diseases and costing the healthcare system billions in treatment, support, and prevention services. A major challenge in the successful treatment of cocaine addiction is reducing the risk of relapse, which remains high after months, or even years of abstinence [6,7].

Animal models of psychiatric diseases are essential to identify

underlying neural circuitry and to test the effectiveness of novel pharmacotherapies to prevent relapse. The extinction-reinstatement model is currently the most commonly used animal model of relapse. In this model, rodents operationally extinguish the drug-seeking response in the drug-associated context [8]. Using the extinction-reinstatement paradigm, researchers have reported that relapse to cocaine-seeking is associated with decreased basal glutamate in the nucleus accumbens (NAc) core [9], as well as enhanced synaptically-released glutamate during drug-primed reinstatement of cocaine-seeking [10]. Additionally, cocaine self-administration and extinction training are accompanied by significant alterations in synaptic plasticity in the NAc, including increased spontaneous excitatory postsynaptic current (EPSC) amplitude and frequency [11]. These findings highlight the glutamate system as a significant contributor to the neural adaptations that underlie the pathophysiology of cocaine addiction. Current research indicates that type 5 metabotropic glutamate receptors (mGluR5) may be of particular importance to the onset and maintenance of cocaine addiction. Thus, the main objective of this literature review is to summarize research focusing on the role of mGluR5 in mouse models of cocaine addiction and assess the potential efficacy of targeting this receptor as a novel therapeutic option to prevent relapse. For background purposes, we also provide an overview of the glutamate system and the various behavioral assays used in addiction research, as well as mouse strain differences specific to cocaine addiction research.

The Glutamate System

Glutamate is the most prevalent excitatory neurotransmitter in the central nervous system, mediating as much as 70% of both fast and slow excitatory neurotransmission [12]. Glutamate receptors are either ligand-gated ion channels (i.e., ionotropic glutamate receptors, iGluRs) or G-protein coupled receptors (i.e., metabotropic glutamate receptors, or mGluRs). iGluRs are ion channels that are permeable to cations and function by allowing Na+ and Ca2+ to enter the cell initiating action potentials and activating various intracellular signaling pathways. iGluRs are located on the head of postsynaptic dendritic spines, mediate fast excitatory neurotransmission, and are divided into three different subtypes: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), and kainic acid (KA) [12]. mGluRs are located on both presynaptic terminals and postsynaptic dendritic spines [13-15]. mGluRs mediate slower, modulatory neurotransmission, and based on their intracellular signaling and pharmacological properties, are categorized into three families. Group I mGluRs consists of mGluR1 and mGluR5 receptors, Group II mGluRs consists of mGluR2 and mGluR3 receptors, and Group III consists of mGluR4, mGluR6, mGluR7 and mGluR8 receptors [12]. Group I mGluRs primarily utilize Gq/G11 signaling mechanisms that activate phospholipase C to form diacylglycerol (DAG) and inositol triphosphate (IP3). DAG activates protein kinase C (PKC), while IP3 exerts further downstream effects by binding to IP3 receptors on the endoplasmic reticulum releasing intracellular Ca2+, which in turn activates other intracellular messengers such as calcium/calmodulin-dependent kinase II (CaMKII). PKC exerts further downstream effects by phosphorylating cAMP response element (CRE) binding protein (CREB) and other signaling molecules, which can eventually lead to altered gene transcription [14]. Other intracellular signaling targets of Group I mGluRs include pathways involving Gi/o and Gs signaling, as well as the mitogen-activated protein kinase/extracellular signal-related kinase (MAPK/ERK) and mammalian target of rapamycin (mTOR)/p70 S6 kinase pathway, both of which are highly implicated in the regulation of synaptic plasticity [16-20]. Group I mGluRs are physically linked to NMDA receptors by various scaffolding proteins (such as Homer, Shank and GKAP) and positively modulate NMDA receptor function. Through its activation of PKC, mGluR5 activation also increases the phosphorylation of NMDA receptor subunits, thereby indirectly increasing the probability of NMDA receptor channel opening [21]. Due to the postsynaptic localization of Group I mGluRs, these receptors primarily initiate and regulate long-term potentiation (LTP) and long-term depression (LTD) by postsynaptic mechanisms such as potentiation of NMDA receptor function [22,23]. These structural and biochemical interactions allow for the stimulation of group I mGluRs to activate NMDA receptors with less risk of inducing excitotoxicity [24,25]. mGluR5 in particular is expressed in both intrinsic and projection neurons in the NAc and the striatum, two key brain regions that influence the behaviors related to psychostimulants [26]. The high prevalence of mGluR5 expression in these areas indicate that mGluR5 activity may modulate information processing, as well as the information that is transmitted from these regions to other brain regions. These findings add support to further investigate the specific role of mGluR5 in cocaine addiction.

Animal Models

Animal models are commonly used in pharmacological research, specifically rodents. Animal models of addiction generally fall into two categories; non-contingent and contingent. Non-contingent includes models such as conditioned place preference where addiction is dependent on the experimenter administering the drug [27], whereas contingent models are based on operant learning and repeated drug exposure by the subject performing an act [27]. An example would be self-administration. Self-administration uses intravenous injection (i.v.) where the animal will administer compounds themselves through a lever press or nose poke. This model is useful as it can be used to represent addiction as the animal has control over the administration.

A common way to test drug seeking behavior is through extinction-reinstatement. Extinction-reinstatement begins with training subjects to self-administer a drug. This is achieved through surgical implantation of a jugular vein catheter and using operant boxes to allow the animal to push a lever or nose poke in order to receive a cue-paired infusion of cocaine (1 mg/kg/infusion). The cue in this phase, usually a tone, low dose of drug, or stress, serves as a conditioned stimulus. This training period includes daily 2 hour sessions that continue until a criterion of ≥10 infusions of cocaine/session for 12 consecutive days is attained [28,29]. After the criterion is reached, rodents begin extinction training. In this phase, lever presses or nose pokes that previously yielded cocaine

and cues (active level/nose poke) no longer do so. Successful extinction is generally defined as an average of <20 active lever presses or nose pokes that previously yielded cocaine and cue for 2 consecutive days. Following this phase, animals are tested for reinstatement, which indicates relapse or drug seeking behavior. The cue-primed reinstatement phase is typically a single 2-hour session. Here, levers/nose pokes, which yielded the conditioned stimulus, that were previously active and paired with drug-delivery now do not infuse the drug. If cue-primed reinstatement re-establishes drug seeking behavior, which is measured by high bouts of lever press/nose poke on previously active levers, then the animal is considered to have reinstated drug seeking behavior that is inferred as relapse [28,29]. This is a very useful paradigm for modeling addiction and is especially useful when examining treatments for addictive substances.

The forced abstinence model of addiction has higher translational value compared to the extinction-reinstatement paradigm but is not as widely used. In this model, animals use the same drug self-administration procedures, but instead of undergoing the extinction procedures, the animals go through withdrawal in a context that is different from the one previously paired with drug use [30]. This model more closely resembles the human experience of drug withdrawal.

Another model is conditioned place preference (CPP). CPP is a non-surgical, simple and affordable paradigm based on classical Pavlovian conditioning that can be used to assess the potential rewarding effects of a drug stimulus, extinction, and drug reinstatement [31,32]. In addiction research, CPP involves repeatedly pairing a rewarding drug stimulus, the unconditioned stimulus (UCS), with a particular context, the conditioned stimulus (CS). Similar to the above behavioral models of addiction, there are a number of different designs that may be implemented when performing CPP. A common apparatus for CPP consists of three compartments. One center compartment with no particular contextual features and a removable gate, which can serve as a connector between two outer compartments that are contextually different from one another. Contextual variations may include differences in floor texture or wall color/design. For example, one outer compartment may have horizontal grid flooring while the opposite outer compartment would have vertical grid flooring. Another example could be wall color, where one outer compartment may have black walls while the opposite outer compartment would have white walls. Procedures for CPP typically begin with 1-3 days of habituation and bias assessment. Here animals are allowed free roam of the entire apparatus for 10-20 minutes. This allows researchers to identify which compartment the animals naturally prefer. Following habituation and assessment for compartment bias, animals begin conditioning procedures. During the conditioning procedures, the gate that connects the two compartments is closed. Animals alternate daily between pairing a drug stimulus with the compartment they least preferred during test bias and a saline injection paired with the compartment they most preferred during test bias. After 8 days of conditioning, animals begin the test preference phase where the gate between the two compartments is removed and animals are allowed free access for a period of time [31,32]. During the test preference phase, if a drug stimulus is perceived as rewarding, the animal's preferred compartment will switch to the compartment associated with the drug stimulus. Extinction may also be examined with CPP, where the animal is allowed to continue free roam of the apparatus for 1-2 weeks with no drug. To assess drug reinstatement, researchers may administer a lower dose of the drug stimulus and allow the animals to free roam. If the animals reinstate, they will spend more time in the compartment previously paired with the drug stimulus [31-35].

Mouse Strain and Cocaine Addiction

For the purposes of this review, we will focus on mouse models in cocaine addiction only. There are two strains of mice used in this field, C57BL/6 and CD-1 IGS (also referred to as ICR; from here on we will refer to this mouse strain as CD-1), with C57BL/6 being preferred when studying cocaine addiction [36]. C57BL/6 mice are an inbred strain that are genetically conserved, whereas the CD-1 mouse strain is considered an outbred or heterogeneous strain. Ruiz-Durantez and colleagues found that when using i.v. cocaine self-administration, 76% of C57BL/6 mice met acquisition criteria, achieving more than 15 injections per session for three consecutive days, where only 19% of CD-1 mice met the same criteria [37]. Additionally, some researchers have cross bred between C57BL/6 and CD-1 mice. These studies report that mice with 75% C57BL/6 genes exhibited an inverted U-shape of self-administration rates, indicating the mice can obtain dose-response sensitivity faster with less restricted access to cocaine [37]. Thus, the strain of mouse is important to consider when modeling cocaine addiction, with C57/BL6 mice appearing to be superior for the study of cocaine addiction. Alternatively, the outbred, CD-1, strain may be a better option for studying resilience to drug addiction.

An additional study performed by McCarthy and colleagues assessed the effect of mouse age and strain (C57BL/6 or CD-1), as well as chronic vs acute administration, on the pharmacokinetics of cocaine [38]. For acute administration, (20 mg/kg, i.p.), researchers found that the early periadolescent age of both strains had lower cocaine blood concentrations compared to adult aged mice, but only the early periadolescent aged C57BL/6 mice had lower cocaine brain concentrations compared to adult aged mice. They also reported that CD-1 early periadolescent and adult mice had significantly lower blood cocaine levels compared to periadolescent and adult C57BL/6 mice. No significant differences were found in brain cocaine levels between late adolescent and adult C57BL/6 mice. For chronic administration (20 mg/kg, i.p. for 7 days), there were no significant differences in cocaine brain concentration between age within strain. However, the cocaine brain levels of early and late periadolescence, as well as adults, were lower in CD-1 mice compared to C57BL/6 mice. They also tested for differences in locomotor activity after an acute dose of cocaine (20 mg/kg, i.p.) and found that CD-1 early adolescents are more active compared to other ages and strains [38]. Results from this study demonstrate that age and strain play a role in the pharmacokinetics of cocaine, and the subsequent effect of cocaine on locomotor function.

During our literature review, we noted a large range of cocaine doses being used, spanning between 1 mg/kg to 30 mg/kg. Interestingly, C57BL/6 mice are more often receiving doses on the higher end of the scale. Doses and details of cocaine administration are listed with all studies we report on.

Cocaine-induced mGluR5 Adaptations by Brain Structure

Basolateral Amygdala

Georgiou and colleagues were the first to demonstrate modulation of mGluR5 following cocaine reinstatement [39]. CD-1 mice underwent the typical cocaine acquisition and extinction-reinstatement procedures as described above. To assess reinstatement, researchers either administered a single (10 mg/kg, i.p.) dose of cocaine and immediately placed the mouse in the operant chamber or presented the conditioned stimulus cue light. Both the cue and drug stimulus reinstated cocaine seeking, with the drug stimulus producing a stronger effect, as measured by significant nose pokes on the hole that previously yielded cocaine. Quantitative autoradiography was performed 24 hours following the reinstatement phase [39]. This data demonstrated a significant decrease in overall mGluR5 binding in the basolateral amygdala compared to saline treated control mice.

Bed Nucleus of the Stria Terminalis (BNST)

Repeated cocaine administration, noncontingent (20 mg/kg, i.p. for 10 consecutive days) and contingent (self-administration), attenuates mGluR5-dependent LTD in the BNST, however a single exposure had no effect in C57BL/6 mice [40,41]. Interestingly, as a follow up study, Gosnell and colleagues reported no changes in total mGluR5 protein expression in the BNST due to chronic cocaine exposure, whether contingent or noncontingent [42].

Hippocampus

Bird et al. examined cocaine self-administration (1 mg/kg/infusion) and extinction in mice that were either mGluR5 +/+ wildtype (WT) or mGluR5-deficent (mGluR5 -/-) C57BL/6 mice [43]. Based on their results they found that mGluR5-deficient mice had a greater preference for cocaine compared to WT mice, and had an impaired ability to extinguish cocaine, requiring more than double the number of extinction sessions compared to the WT mice. Overall, they suggest that this deficit caused impairments to behavioral flexibility, particularly relating to context and presence of cocaine, along with action to overcome relationships. Using a Morris water maze task, which measures spatial learning and is highly dependent on the hippocampus, they found that mGluR5-deficient mice took longer to learn compared to WT mice. These findings indicate that mGluR5-deficient mice may have impaired hippocampal function. Additionally, results demonstrate a deficit in LTP that may result from AMPA and NMDA receptor-mediated components, specifically within the CA1 region of the hippocampus [43].

Hypothalamus

In C57BL/6 mice that were either WT or mGluR5-deficient, Stoker and colleagues assessed anhedonic aspects of spontaneous cocaine withdrawal [44]. Stimulating electrodes were placed within the lateral hypothalamus of mice and were trained to perform Intracranial Self-Stimulation (ICSS). They were given saline or cocaine (180 mg/kg/day, i.p.) for 3 days and tested daily for ICSS threshold and response latencies. Minipumps were then removed, and they were tested on the ICSS procedure. Researchers found that ICSS thresholds during withdrawal for cocaine mice were significantly higher than the saline mice. As well as WT mice showing elevated threshold compared to mGluR5-deficient mice during chronic cocaine withdrawal. This indicated that mGluR5-deficient mice have attenuated anhedonic aspects of cocaine withdrawal [44].

Nucleus Accumbens (NAc)

An important brain structure involved in addiction is the NAc; the core is associated with instrumental learning, such as cue-induced drug seeking [45], and the shell is responsible for the primary reinforcing effects of addictive drugs [46]. There are mixed findings regarding cocaine-induced adaptations to mGluR5 levels in the NAc. Huang et al. administered cocaine (15 mg/kg, i.p.) for 5 consecutive days followed by 14 days of withdrawal [47,48]. They found mGluR5 protein levels were decreased selectively in the shell, but not in the core, of the NAc in cocaine-treated C57BL/6 mice. The decrease of mGluR5 expression in the NAc shell was accompanied by impaired mGluR5-dependent LTD, which was not observed in the NAc core [47,48].

Contradicting Huang and colleagues findings [47,48], Ary and Szumlinski found no change in mGluR5 levels in the NAc shell following 7 consecutive days of cocaine (30 mg/kg, i.p.) administration followed by 21 days of withdrawal [49]. These differences are likely due to discrepancies in methodology, as the dose, duration of treatment, and the withdrawal time are all significantly different between the two studies. In another discrepancy to Huang and colleagues findings, Georgiou and colleagues reported an increase in mGluR5 binding in the NAc core in mice that had undergone cocaine self-administration, extinction, and both cue and drug-primed reinstatement [39].The different findings between these two studies are also likely due to differences in methodology.

PreFrontal Cortex (PFC)

The PFC is the brain region responsible for critical aspects of executive functions, such as working memory and attention. Sidiropoulou and colleagues identified a link between cocaine-induced mGluR5 adaptations and PFC impairment [50]. mGluR5 was expected to play a mechanical role in the impairment of PFC-dependent executive functions as the inhibition of mGluR5 has previously been linked to impaired working memory [51]. Sidiropoulou and colleagues used voltage- and current-clamp recording to study Ca2+-dependent postsynaptic mGluR-mediated delayed afterdepolarization (dADP) in layer 5 of the PFC in WT and mGluR1 and mGluR5-deficient C57BL/6 mice following 5 days of repeated cocaine treatment (15 mg/kg, i.p.) and a 2 day withdrawal period [50]. After isolating selective mGluR agonist (RS)-3,5-dihydroxyphenylglycine (DHPG)-induced current (IDHPG) and dADP in the PFC, they found no difference between

mGluR1-deficient mice compared to WT littermates but found a complete attenuation of IDHPG and burst-elicited dADP in mGluR5-deficient mice compared to WT littermates. These results indicate that mGluR5 is a key mediator for sustained PFC activity and that this mechanism is impaired during withdrawal after repeated cocaine use [50].

Additional research examined the alteration of mGluR5 in the PFC of mice due to cocaine administration. Glutamatergic cells in the PFC are activated by both cocaine and glutamate, causing drug-associated responses such as locomotor sensitization, drug seeking, and conditioned responses to drug-associated stimuli [52]. Using an open field locomotion task, C57BL/6 mice were given acute or chronic i.p. injections of either saline-saline, cocaine-saline, or cocaine-cocaine (10 mg/kg acute or 20 mg/kg for 5 consecutive days); results indicate that as the dose of cocaine increased, so did the locomotor activity and the mRNA expression of mGluR5 in the PFC [53].

Substantia Nigra

Looking at the interaction between mGluR1 and mGluR5, Kramer and Williams used WT C57BL/6 and C57/129 (a hybrid between 129S1/SlmJ (inbred) and C57BL/6 mice) mice [54]. They administered cocaine (20 mg/kg, i.p.) and assessed whole cell readings of mGluR5 expressing dopamine neurons in the substantia nigra par compacta. They used a selective mGluR agonist, DHPG, and apamin to block calcium-activated potassium (SK) conductance and to isolate mGluR-mediated currents. From this they found a reduction in mGluR1-dependent currents and no change in mGuR5-dependent currents after a single cocaine injection. To determine specific receptor roles, researchers administered a pharmacological blockade of mGluR5 prior to the cocaine injection and found a decrease in cocaine-induced mGluR1-dependent currents. These findings indicate that activation of mGluR5 after administration of cocaine is necessary to produce the cocaine induced decrease of mGluR1 signaling in the striatum [54].

Ventral Tegmental Area (VTA)

Bird et al. used mGluR5-deficient and WT C57BL/6 mice. Mice were administered cocaine (20 mg/kg, i.p.) or saline, and 24 hours later brains were harvested for sectioning of the VTA [55]. Results demonstrate that mice lacking mGluR5 did not produce AMPA/NMDA EPSC amplitude ratio within the excitatory synapses of the VTA dopaminergic neurons [55]. This indicates that mGluR5 may be important for the signaling cascade caused by cocaine administration. The second part of this experiment was to test locomotor behavior. Researchers administered cocaine (20 mg/kg, i.p.) and placed mice in a novel environment and recorded for 30 minutes for five days. They found an increase in locomotor activity in mGluR5 deficient mice, which contradicts the findings of Chiamulera et al. who did not find an increased locomotor response to cocaine in mGluR5 deficient mice [55,56].

Potential Pathways/interactions

Several brain areas and neural pathways integrate to drive addictive behaviors. In this section, we summarize the neural interactions that may affect cocaine-induced mGluR5 adaptations. From the articles cited above, the most heavily involved include additional glutamate receptors, such as mGluR1, AMPA, & NMDA, and the dopamine and endocannabinoid systems.

As discussed earlier, mGluR1 and mGluR5 function is closely intertwined as they are both characterized as group 1 metabotropic glutamate receptors. Kramer and Williams demonstrated this relationship through whole cell recording [54]. They determined that cocaine treatment downregulates mGluR1 through activation of mGluR5. They first treated mice with cocaine and observed a decrease in mGluR1, but not mGluR5 signaling, in substantia nigra dopamine neurons. They next activated mGluR5 with DHPG, which had the same effect as cocaine on mGluR1 current. As a last step, they blocked mGluR5 prior to cocaine administration, which inhibited the effect of cocaine on mGluR1 current. These results clearly outline the important relationship between mGluR1 and mGluR5 in the effects of cocaine [54]. NMDA and AMPA receptors also play a critical role as they strongly modulate LTD and LTP mechanisms that underlie synaptic plasticity. It is well-established that acute administration of cocaine causes a significant increase in AMPA/NMDA EPSC amplitude ratios [57,58]. In 2010, Bird and colleagues reported that cocaine-induced potentiation of AMPA/NMDA EPSC amplitude ratios of dopamine neurons in the VTA is absent in mGluR5 deficient mice [55]. These results indicate that mGluR5 signaling is necessary for acute cocaine-induced plasticity at excitatory synapses of dopaminergic cells in the VTA [55]. In 2014, Bird and colleagues reported impaired LTP in the CA1 of the hippocampus in mGluR5 deficient mice. This is likely due to the modulation of both AMPA and NMDA receptor-mediated components [43]. There are both glutamatergic and dopaminergic pathways between the VTA and CA1. VTA glutamate neurons influence CA1 excitability and burst pairing, while VTA dopaminergic neurons influence CA1 firing patterns [59]. Although this connection has yet to be thoroughly explored under cocaine conditions.

The dopamine system has long been implicated in the acquisition and maintenance of cocaine addiction. Of interest, is how mGluR5 modulation may affect dopamine signaling and the cumulative effect on cocaine addiction. Novak and colleagues examined the role of mGluR5 and dopamine D1 receptors (D1R) in cocaine-seeking behavior [60]. Using cell type-specific RNA interference, they generated a mutant mouse strain in which mGluR5 is selectively knocked down in neurons expressing D1R. Following cocaine extinction-reinstatement procedures, they found that mutant mice had reduced cue reinstatement. This highlights the potential role of mGluR5 as a mediator of reinforcement learning. To follow up, researchers studied the ability of mutant mice to perform associative learning. Mutant mice were able to learn the predictive properties of reward-paired stimuli, such as the availability and location of a reward, but displayed deficits in learning incentive motivational properties that allow a reward to attract attention and directly reinforce instrumental behaviors. These results indicate that mGluR5 activity on D1R-expressing

neurons in the NAc is essential for reward learning that facilitates cue-induced reinstatement of cocaine-seeking [60].

There is also evidence that endocannabinoids (eCB) play a role in cocaine abuse. Exploring the potential pathways involved, cocaine induced behavioral sensitization creates a decrease in excitatory drive to the NAc and reduces production of NAc basal extracellular glutamate [61]. eCB-mediated retrograde long-term depression (eCB-LTD) may play a role in the negative feedback loop at PFC-NAc synapses. These connections seem to reduce the strength of excitatory synapses as seen by the abolishment of eCB-LTD within the NAc of cocaine exposed mice and could counteract the decrease of glutamatergic activity that appears in response to cocaine. Additional research, exploring the link between cocaine induced plasticity within the NAc shell and contextual reinstatement reward-seeking, found a link between plasticity and behavior as conditioned reward behavior is reinstated by direct infralimbic cortex-to-NAc shell pathway stimulation and causes rapid reduction in synaptic strength [62]. Additionally, Fourgeaud and colleagues proposed that single administration of cocaine results in an increase of CC-Homer expression, while repeated exposure decreases CC-Homer expression as it triggers a reduction mechanism [61]. They also suggest that the increase of CC-Homer causes a loss of postsynaptic surface mGluR5, which prevents retrograde signaling of eCB [61].

Novel Therapies Targeting mGluR5

Novel therapeutic targets are at the forefront of drug addiction research. In relation to the articles cited in this review, there are several examples that offer compelling evidence to continue exploring mGluR5 as a therapeutic target for cocaine addiction. From a behavioral perspective, addiction is essentially a learned behavior that is based on repeated exposure to a substance the subject perceives as rewarding. Interestingly, mGluR5 plays a role in the incentive learning process. O'connor et al. administered a non-competitive mGluR5 antagonist, 3-((2-methyl-1, 3-thiazol-4-yl)ethynyl)pyridine (MTEP, 10 mg/kg, i.p.) to C57BL/6 mice and observed the effect on different learning processes [63]. They found that MTEP, when administered before conditioning sessions, prevented conditioned reinforcement on test day. Furthermore, administration of MTEP before conditioned reinforcement testing in mice previously treated with saline prior to conditioning sessions resulted in conditioned reinforcement. This points to the importance of mGluR5 in the acquisition of incentive learning [63]. Benneyworth and colleagues used CPP and cocaine-primed reinstatement in C57BL/6 mice to further examine the role of mGluR5 in drug seeking behavior [62]. Cocaine-conditioned mice were all administered cocaine (7.5 mg/kg, s.c.) for drug-primed reinstatement testing. Following cocaine administration, mice were given either MTEP (3 ug), the mGluR5 selective agonist (R,S)-2-chloro-5-hydroxyphenylglycine (CHPG) (6 ug), or vehicle via bilateral intra-NAc shell microinfusion (0.5 ul/hemisphere at 0.1 ul/minute). This was given 15 minutes prior to reinstatement testing. Treatment with MTEP decreased drug-primed reinstatement, while treatment with CHPG increased drug-primed reinstatement. After the behavior experiments, brains were harvested and the NAc shell sectioned for recording of AMPA/NMDA amplitude ratios and miniature EPSC (mEPSC). MTEP blocked cocaine-induced reduction of mEPSC amplitude and frequency, and CHPG further enhanced cocaine-induced reduction of mEPSC amplitude and frequency. These results demonstrate that mGluR5 is necessary for cocaine-primed reinstatement and cocaine-induced depotentiation in the NAc shell [62].

A second mGluR5 antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), has also been reported to prevent cocaine-induced reduction of mESPC frequency, although not amplitude, in the BNST [41]. This same study reports that repeated cocaine administration (10 days, 20 mg/kg, i.p.) disrupted DHPG-induced LTD (DHPG-LTD). Within this study it is important to note they found days 1, 3, and 5 of cocaine administration was not enough to disrupt DHPG-LTD, and that after 10 days of withdrawal, DHPG-LTD was normal. Administration of MPEP prior to cocaine prevented cocaine-induced disruption of DHPG-LTD [41]. Kramer and Williams found that a single cocaine injection (20 mg/kg, i.p.) decreased mGluR1 currents in dopaminergic neurons of the substantia nigra, and pretreatment with MPEP (30 mg/kg, i.p.) was able to prevent that decrease [54]. The mGluR5-negative allosteric modulator fenobam (30 mg/kg, i.p.) was also able to attenuate cocaine and cue-induced reinstatement in C57BL/6 mice [47].

McGeehan and Olive, assessed whether MPEP could reduce the rewarding effects of different drugs [35]. They found when C57BL/6 mice and DBA/2J mice (an inbred mouse strain that has contrasting characteristics to C57BL/6 mice) were treated with MPEP (1, 5, and 20 mg/kg, i.p.) 10 minutes prior to receiving cocaine (15 mg/kg, i.p.), they had reduced CPP compared to mice that received other drugs (D-amphetamine (2 mg/kg, i.p), nicotine (0.5 mg/kg, i.p.), morphine (5 mg/kg, i.p.), or ethanol (2 mg/kg, i.p.). These results support the notion that mGluR5 plays a specific role in the rewarding effects of cocaine that cannot be generalized to other addictive substances [35]. Cumulatively, the research cited in this section presents behavioral and cellular data that negative modulation of mGluR5 is a viable therapeutic target for cocaine addiction.

Discussion

Cocaine administration in mouse models induces a range of neural changes in the brain, reflecting the neuroadaptations associated with cocaine addiction. Cocaine-induced mGluR5 adaptations vary by brain region and by methodological constraints. In CD-1 mice that had undergone self-administration, extinction, and cocaine-induced reinstatement (10 mg/kg, i.p.), researchers report an overall decrease in mGluR5 binding in the basolateral amygdala [39]. In the PFC, researchers found that as the dose and duration of cocaine administration increased, so did mRNA levels of mGluR5 (10 mg/kg, i.p., acute; or 20 mg/kg, i.p. for 5 days) [53]. There are mixed findings regarding cocaine-induced adaptations to mGluR5 levels in the NAc. It is important to note that the route of administration, dose, and duration of cocaine treatment influences the adaptations that occur in the mouse brain. In studies performed by Huang and colleagues, they reported

no change in mGluR5 expression in the NAc core or mGluR5-dependent LTD, and decreased expression of mGluR5 in the NAc shell that was accompanied by reduced mGluR5-dependent LTD in C57BL/6 mice that were administered cocaine for 5 consecutive days followed by 14 days of withdrawal [47,48]. Greuter et al. also found a decrease in mGluR5-mediated LTD in the NAc following cocaine administration, although they did not differentiate between the shell and the core [40]. In contradiction to Huang et al. findings [47,48], Ary and Szumlinski found no change in mGluR5 levels in the NAc shell following 7 consecutive days of cocaine (30 mg/kg, i.p.) administration followed by 21 days of withdrawal [49]. These differences are likely due to discrepancies in methodology, as the dose, duration of treatment, and the withdrawal time are all significantly different between the two studies. In another discrepancy to Huang and colleagues [47,48], Georgiou and colleagues reported an increase in mGluR5 binding in the NAc core in mice that had undergone cocaine self-administration, extinction, and both cue and drug-primed reinstatement [39]. The different findings between these two studies are also likely due to differences in methodology. Increased mGluR5 expression and signaling due to cocaine administration in the NAc and PFC may contribute to the enhanced responsiveness to drug-associated cues and the persistence of drug seeking behavior during withdrawal.

Key neural changes that occur in the mouse brain following cocaine administration include adaptations in the dopaminergic and glutamatergic systems. The interplay between mGluR5 and the dopamine system plays a significant role in the neurobiological adaptations that drive cocaine addiction. mGluR5 activation can modulate the activity of dopamine receptors, such as D1, influencing downstream signaling pathways. Evidence of this was reported by Novak and colleagues [60]. Through the development of a mutant mouse strain in which mGluR5 was selectively knocked down in neurons expressing D1R, they determined that mGluR5 activity was necessary for reward learning. In this study, mutant mice were able to learn the predictive properties of reward-paired stimuli, but displayed deficits in learning incentive motivational properties that would allow for cue-induced reinstatement of cocaine-seeking [60]. Thus, modulating mGluR5 signaling may offer a means to regulate dopamine release and signaling, potentially mitigating addictive behaviors and reducing the risk of relapse. This research highlights the complex interactions between the glutamate and dopamine systems, which contribute not only to the rewarding effects of cocaine, but also to the development of addictive behaviors through incentive learning.

Cocaine-induced alterations involve modifications in the strength and connectivity of excitatory synapses, primarily mediated by changes in glutamate receptors, such as AMPA and NMDA receptors. In support of this statement, researchers report an overall decrease in mGluR5 dependent LTD in the BNST, hippocampus, NAc, PFC, and the VTA due to chronic cocaine administration [40,41,43,47,48,50,55]. Understanding the changes in mGluR5 that occur following cocaine administration in the mouse brain provides insights into the molecular mechanisms underlying cocaine addiction. The literature reviewed here further highlights the role of mGluR5 in mediating synaptic plasticity, dopamine signaling, and the development of addiction-related behaviors.

MTEP and MPEP are two selective antagonists of mGluR5 that have been studied for their potential therapeutic effects on mouse models of cocaine addiction. MTEP and MPEP reduce the conditioned responses to drug-associated cues and reduce the motivation to seek cocaine, thereby inhibiting relapse-like behavior [35,62,63]. MTEP and MPEP have been found to modulate synaptic plasticity in brain regions involved in addiction, such as the NAc and PFC [41,52,64]. Overall, MTEP and MPEP demonstrate promising effects in mouse models of cocaine addiction by targeting mGluR5 and modulating neural circuitry and behavior to prevent relapse.

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