Cocaine-mediated synaptic potentiation is absent in VTA neurons from mGlu5-deficient mice

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Abstract

Drugs of abuse have the ability to instantiate plastic adaptations within the central nervous system, and this property may relate to the development and persistence of addiction. In this context, a single exposure to cocaine in rodents may induce synaptic plasticity by increasing the AMPA/NMDA receptor excitatory post-synaptic current (EPSC) amplitude ratio in dopaminergic cells of the ventral tegmental area (VTA). Here, we examine the role of the metabotropic glutamate 5 (mGlu5) receptor in this regard using a genetic mouse model. The control AMPA/NMDA EPSC ratio is reduced in mGlu5-deficient mice compared to wild-types. Moreover, cocaine-induced enhancement of this EPSC ratio is also absent in mutant mice, which suggests that mGlu5 receptors are required for single-dose cocaine-induced plasticity onto VTA cells. While the temporal profile of hyperactivity to acute cocaine is altered in mGlu5-deficient mice; these mice still develop and express sensitized psychomotor responses to cocaine. These data suggest that the mGlu5 receptor is required for cocaine-induced plasticity in VTA dopaminergic cells. In contrast, the mGlu5 receptor may not be essential for psychostimulant behavioural sensitization; although it probably impacts other aspects drug addiction, such as motivation to self-administer.

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Introduction

Ramon y Cajal first suggested that plasticity in the synaptic connections between neurons in the brain is involved in data storage (Ramon y Cajal, 1894). There is now general consensus that the development of addiction may depend, in part, on drug-induced synaptic plasticity in neural pathways that are involved in a range of survival functions including natural reward, learning and memory (Dackis & O’Brien, 2001; Hyman \textit{et al.} 2006; Kalivas & O’Brien, 2007; Nestler, 2001; Thomas \textit{et al.} 2008).

Repeated cocaine administration results in long-term anatomical and signalling changes in neurotransmitter pathways (Horne \textit{et al.} 2008; Robinson & Kolb, 1999) and also behavioural modification in the form of psychomotor sensitization (e.g. Pierce & Kalivas, 1997). Even after acute cocaine administration, lasting synaptic plasticity was observed in the ventral tegmental area (VTA), but not the hippocampus, indicating that specific, drug-induced neuronal adaptations in the mesolimbic system had occurred (Ungless \textit{et al.} 2001). D\textsubscript{1} receptors appear critical for the development of sensitization to systemic amphetamine (Vezina, 1996), while NMDA-mediated signalling onto D\textsubscript{1} receptor-containing neurons of the basal ganglia is implicated in the development of sensitization to cocaine (Heusner & Palmiter, 2005). Low dose intra-VTA injections of the D\textsubscript{2} antagonist eticlopride elevated extracellular dopamine levels within the VTA and enhanced the locomotor response to subsequent
ampheta
mine challenge, linking dopaminergic ac
tivity and behavioural sensitization (Tanabe et al.
2004). Microinjection studies suggested that gluta
mate-mediated plasticity of tegmental dopaminergic
neurons is required in the development of sensitiz
ation to psychostimulants and other drugs of abuse (see
Vanderschuren & Kalivas, 2000, for review). However,
although cocaine-induced plasticity is absent in mice
lacking the GluR1 subunit of the AMPA receptor, be
havioural sensitization to cocaine is not abolished in
these mice (Dong et al. 2004). Furthermore, despite a
strong correlation between increased AMPA/NMDA
excitatory post-synaptic current (EPSC) amplitude ra
tio in the VTA and locomotor hyperactivity to acute
and repeated cocaine, this correlation is transient,
as the expression of sensitized behaviour outlasts
measured alterations in synaptic plasticity (Borgland
et al. 2004). Interestingly, rats in withdrawal after co
caine self-administration display enduring poten
tiation of AMPA/NMDA receptor EPSC amplitude ra
tios in the VTA, a phenomenon not observed after
food or sucrose self-administration (Borgland et al.
2004; Chen et al. 2008). Thus, it appears that drug
induced increases in synaptic strength of VTA cells
may be more closely related to the motivational drive
to self-administer the drug rather than behavioural
sensitization. Preventing drug-induced long-term po
teniation (LTP)-like plasticity in the VTA can dimin
ish the reinforcing properties of drugs of abuse,
inhibiting both conditioned place preference and self
administration behaviours (for a review on the role of
synaptic plasticity in addiction see Kauer & Malenka,
2007).

The metabotropic glutamate 5 (mGlu5) receptor
has been implicated both in natural (Lu et al. 1997)
and drug-induced plasticity (Mameli et al. 2007). Mice
devoid of mGlu5 receptors reportedly fail to self-ad
minister cocaine while they will self-administer a
natural reinforcer (Chiamulera et al. 2001), and also
show reduced voluntary consumption and preference of
alcohol, but not saccharin (Bird et al. 2008). More
over, antagonists of the mGlu5 receptor can prevent
drug-seeking behaviour in rodent models of relapse
(Adams et al. 2008; Backstrom et al. 2004; Hodge et al.
2006). In contrast, pre-treatment of rodents with
selective mGlu5 receptor antagonists does not prevent
the development of sensitization to psychostimulants
(Yap et al. 2005). The present study was therefore
designed to address (i) whether cocaine-induced VTA
plasticity (increases in the AMPA/NMDA receptor
EPSC amplitude ratio) occurs in mGlu5-deficient mice
and (ii) if deletion of the mGlu5 receptor regulates
behavioural sensitization.

Materials and methods

Ethics and animals

All experiments were performed in accordance with
the Prevention of Cruelty to Animals Act, 1986 under
the guidelines of the National Health and Medical
Research Council (NHMRC) Code of Practice for the
Care and Use of Animals for Experimental Purposes
in Australia. mGlu5-deficient mice (Lu et al. 1997) on
a C57BL/6J background (Grm5tm1Bood; stock 003558)
were obtained from Jackson Laboratories (Bar Harbor,
USA). A heterozygous breeding colony was estab
lished by crossing mGlu5+/− mice with C57BL/6J
wild-type mice from Animal Resources Centre (Perth,
Australia). This strategy ensured the provision of
wild-type littermates as control subjects. The genotype
of individual mice was determined by PCR and
immunohistochemistry as previously described (Bird
et al. 2008). All mice were given free access to food and
water in home cages, and were maintained on a 12-h
light/dark cycle (lights on 07:00 hours). All behav
ioural experiments were conducted using male mice
aged between 8 and 12 wk, age-matched for each ex
periment. Electrophysiological recordings used mice
aged between 16 and 21 d.

Electrophysiological studies

Preparation of acute slices

Mice were injected with saline (10 ml/kg i.p.) or co
caine (20 mg/kg i.p.). Twenty-four hours later, mice
were decapitated and brains were rapidly removed
and immersed in ice-cold artificial cerebrospinal fluid
(ACSF; composition (mM): 125 NaCl, 3 KCl, 6 MgCl2,
1 CaCl2 1.25 NaH2PO4, 25 NaHCO3 10.6 glucose, satu
rated with 95% O2/5% CO2. A block of tissue contain
ing the midbrain was sliced at 300 μm in the horizontal
plane and then placed in a holding chamber for at least
1 h as previously described (Reid & Clements, 1999;
Tan et al. 2007).

Electrophysiological recording

Slices were transferred to the recording chamber and
superfused with ACSF (32–34 °C) saturated with 95%
O2/5% CO2 and containing (mM): 125 NaCl, 3 KCl, 1
MgCl2, 2 CaCl2, 1.25 NaH2PO4, 25 NaHCO3, 10.6
glucose. Picrotoxin (50 μm; Sigma, USA) was added to
the ASCF to block GABA A-mediated inhibition. VTA
dopamine cells were visualized using an infrared DIC
microscope (BX51, Olympus) and whole-cell patch
clamp recordings were obtained using patch pipettes
(1.5–3 MΩ) fabricated from borosilicate glass capil
laries (Warner Instruments, USA). The electrodes were
filled with intracellular saline solution [composition (mM): 105 CsCl, 40 D-mannitol, 10 Hepes, 10 EGTA, 10 phosphocreatine, 4 MgATP and 0.3 NaGTP (pH 7.3–7.4), 285–295 mOsm]. Biocytin (0.03%, Sigma) was included in the internal solution for post-hoc identification of recorded neurons. Currents were recorded with a HEKA EPC10 amplifier and experimental control and data acquisition performed with Patchmaster software (HEKA Elektronik, Germany) and analysed using Axograph software packages (Axograph X, Australia). Passive electrical properties of neurons recorded from each experimental group were similar. Capacitance was used to estimate neuron size with those having a capacitance of < 30 pF excluded from analysis. Stimuli (single 40–100 μs duration pulses) were delivered via a sharpened monopolar tungsten-stimulating electrode (A-M Systems, Australia). Neurons were clamped at a membrane potential of −70 mV except where noted. AMPA receptor-mediated EPSC amplitudes were measured at +40 mV holding potential in the presence of the NMDA receptor antagonist D(-)-2-amino-5-phosphonopentanoic acid (APV, 50 μM), by averaging over a 1-ms window around the peak. A 20-ms average baseline measured just prior to stimulation artefact was subtracted. NMDA receptor-mediated EPSCs were measured at +40 mV from traces in which AMPA receptor-mediated currents had been digitally subtracted post-hoc. The EPSC amplitudes were measured by averaging over a 15-ms window after subtracting the average baseline. Between 5 and 10 traces were averaged for each recorded neuron. Typically, two neurons were recorded from slices obtained from a single mouse. A total of 10 wild-type and 10 mGlu5-deficient mice were used for recordings.

**Morphological identification**

After fixing overnight with 4% paraformaldehyde, slices were rinsed with PBS, permeabilized with 0.3% Triton-100 and then incubated with 1% normal goat serum and streptavidin-Alexa Fluor594 (1:200; Invitrogen, USA) for 2.5 h. Rinsed slices were mounted onto slides using fluorescence mounting medium (Dako, USA) for visualization.

**Behavioural studies**

**Locomotor behaviour – novel environment**

The effect of genotype on locomotor activity in response to exposure to a novel environment was examined using TruScan™ photobeam activity monitors (Coulbourn Instruments, USA), essentially as previously described (Brown et al. 2009; Cowen et al. 2005; McPherson & Lawrence, 2006). Monitoring was performed once per day for three consecutive days over a 30-min period using the TruScan software. This cohort of mice was subsequently used for cocaine locomotor studies (see next section).

**Locomotor behaviour – cocaine**

The effect of genotype on both the acute and sensitized response to cocaine (cocaine hydrochloride, Sigma) was assessed in wild-type and mGlu5-deficient mice using TruScan photobeam activity monitors. After 3 d habituation to the locomotor equipment to reduce the novelty of the monitoring environment, mice were divided into two groups which underwent five consecutive days of chronic treatment with either cocaine (20 mg/kg i.p.) or vehicle (0.9% saline, 10 ml/kg i.p.), with locomotor activity being recorded for 30 min following each injection. All mice were subsequently confined to home cages for 7 d with free access to food and water. On the challenge day, each group of mice was subdivided into a cocaine (10 mg/kg i.p.) and vehicle (0.9% saline, 10 ml/kg i.p.) cohort, resulting in a total of four groups per genotype. This experimental design allowed detailed and controlled examination of the cocaine behavioural phenotype in mGlu5-deficient mice; saline pre-treatment/saline challenge (basal control), saline pre-treatment/cocaine challenge (response to acute cocaine exposure), cocaine pre-treatment/saline challenge (contextual influence on behaviour observed on challenge day) and cocaine pre-treatment/cocaine challenge (expression of sensitized behaviour).

**Statistical analyses**

Electrophysiological data were analysed using Student’s two-tailed unpaired t test. Behavioural data were analysed using two-way (genotype x time), three-way (genotype x treatment x time-point) or four-way (genotype x pre-treatment x challenge treatment x time-point) repeated-measures analysis of variance (ANOVA), with Tukey post-hoc tests where appropriate. In all cases, significance was accepted where p < 0.05. Note that for the sake of simplicity, only pertinent effects and interactions have been included.

**Results**

**Cocaine increases synaptic strength in wild-type but not mGlu5-deficient VTA dopamine neurons**

Cocaine (20 mg/kg i.p.) or saline (0.9% saline, 10 ml/kg i.p.) were administered 24 h prior to cutting of
the recorded cell which was held at +40 mV. Following stable recordings, the NMDA receptor antagonist, APV (50 μM), was added to the perfusate to isolate AMPA receptor-mediated EPSCs. The NMDA receptor component of the EPSC was obtained by digital subtraction to enable calculation of AMPA/NMDA receptor EPSC amplitude ratios (Fig. 1). Several previous studies demonstrate an effect of single-dose cocaine on this ratio (Borgland et al. 2004; Ungless et al. 2001). The present study replicated these results, showing a significant increase in the AMPA/NMDA receptor EPSC amplitude ratio in neurons from wild-type mice following cocaine injection (Fig. 1b, p < 0.05, unpaired t test). In contrast there was no change in the AMPA/NMDA receptor EPSC amplitude ratio for mGlu5-deficient animals following cocaine injection (Fig. 1c, p = 0.3, unpaired t test). Interestingly, differences in the AMPA/NMDA receptor EPSC amplitude ratio were observed between saline-treated wild-type and mutant animals (wild-type 1.39 ± 0.15, n = 9; mGlu5-deficient 0.88 ± 0.12, n = 7; p < 0.05, unpaired t test).

**mGlu5-deficient mice display normal development but attenuated expression of sensitization to cocaine**

Upon exposure to a novel environment, mGlu5-deficient mice were hyperactive compared to wild-type littermates (F_{1,22} = 46.479, p < 0.001; Fig. 2a); however, habituation occurred with subsequent re-exposures, such that no genotype difference was observed on the third experience of the locomotor cells (Fig. 2b).

Following acute cocaine (20 mg/kg) administration, a main effect was observed for treatment (F_{1,11} = 46.479, p < 0.001) but not for genotype, indicating that both wild-type and mGlu5-deficient mice displayed a similar overall increase in locomotor activity when treated with cocaine compared to vehicle (Fig. 2c). However, a significant interaction between treatment, genotype and time-point (F_{5,55} = 2.323, p = 0.042) was also observed, indicating a differential in the temporal response to treatment between the genotypes. Further examination of this interaction indicated that wild-type mice reached peak activity within the first 5 min following injection of cocaine, while mutant mice displayed a distinct delay in the onset of cocaine-induced hyperlocomotion (Fig. 2d). This is supported by a significant difference between the genotypes in the first 5 min of the acute cocaine time-course as detected by a Tukey post-hoc test (q = 3.297, p = 0.022).

In order to assess the development of sensitization to cocaine, mice of both genotypes were treated with
cocaïne for five consecutive days and locomotor activity assessed on each occasion. In terms of total activity for each day over the treatment period, there was a significant effect of day \( (F_{4,256} = 13.926, p < 0.001) \), and of genotype \( (F_{1,64} = 4.136, p = 0.046) \), but no interaction between these two factors (Fig. 3). This indicates that although there was an overall difference between the genotypes (due to a large time \( \times \) genotype interaction: \( F_{5,1280} = 23.435, p < 0.001 \)), both genotypes followed a similar pattern in developing sensitization to cocaine.

After a 7-d withdrawal period, mice were injected with either cocaine (10 mg/kg) or saline and then re-introduced into the locomotor cells to examine expression of sensitization (Fig. 4). A main effect was observed for both pre-treatment \( (F_{1,186} = 13.544, p < 0.001) \) and challenge treatment \( (F_{1,164} = 33.294, p < 0.001) \), but not of genotype. This indicates that both genotypes expressed similar sensitized behaviour on challenge day, supporting the previous observation that both genotypes developed sensitization to a...
similar degree over the pre-treatment period. Interestingly, sensitized mGlu5-deficient mice (Fig. 4b) demonstrated a similar temporal profile of locomotor activity as wild-type mice (Fig. 4a). This is in contrast to the acute challenge (saline/cocaine) group where peak hyperactivity was again delayed in mutant mice, replicating the locomotor profile observed following acute exposure to 20 mg/kg cocaine (Figs 2d, 4b).

Comparison of the relative difference within genotypes between the control groups (saline/saline vs. cocaine/saline) upon challenge suggests that contextual re-exposure to the locomotor cell had a greater impact upon mGlu5-deficient mice than wild-types (Fig. 4). Such an effect would probably be obscured in the above four-way repeated-measures ANOVA due to the dramatic effect of cocaine on challenge day. This is an important consideration, given that gross behaviour with regard to locomotor sensitization is a composite of a contextual response to a previously drug-associated environment and actual drug-induced adaptation. For this reason we examined the effect of pre-treatment on the behavioural response to saline on challenge day (three-way repeated-measures ANOVA, genotype \times pre-treatment \times time). In this instance, there was a main effect of pre-treatment ($F_{1,59} = 20.591$, $p < 0.001$), plus a significant interaction between genotype \times pre-treatment ($F_{1,59} = 6.597$, $p = 0.013$). Thus, locomotor activation in the cocaine/saline group compared to the saline/saline group was greater in mGlu5-deficient mice compared to wild-types. This would suggest the response to contextual re-exposure is exaggerated in mGlu5-deficient mice compared to wild-type littermates.

**Discussion**

Here we report that the cocaine-induced potentiation of AMPA/NMDA EPSC amplitude ratios at excitatory synapses of VTA dopaminergic neurons is absent in mice lacking mGlu5 receptors. In contrast, recordings from slices taken from wild-type littermates recapitulate previous findings (Borgland et al. 2004; Ungless et al. 2001). This observation suggests that mGlu5 receptors are required for single-dose cocaine-induced plasticity at excitatory synapses of dopaminergic cells in the VTA. Behavioural studies highlighted that while the temporal profile of hyperactivity to acute cocaine challenge is altered in mGlu5-deficient mice, these mice retain the ability to develop and express sensitized psychomotor responses to cocaine.

Group I mGlu receptors, and more specifically mGlu5 receptors, have been implicated in the induction of LTP in layer V pyramidal cells of the cortex (Sourdet et al. 2003), hippocampal CA1 neurons (Jia et al. 1998; Lu et al. 1997) and lateral amygdaloid cells (Fendt & Schmid, 2002). Consequently, mGlu5 receptors have been linked to learning, memory and the acquisition of conditioned fear. In addition, the mGlu5 receptor has also been implicated in aspects of drug abuse, including self-administration of cocaine (Chiamulera et al. 2001) and alcohol (Bird et al. 2008; Blednov & Harris, 2008). The present study is at odds
with a previous report showing that cocaine did not induce locomotor hyperactivity in mGlu5-deficient mice (Chiamulera et al. 2001). This may relate to the fact that the studies were performed on different background strains (Swiss and C57Bl/6J) and the mice were derived from different gene targeting approaches. Furthermore, pharmacological studies employing antagonists that do not discriminate between mGlu receptor subtypes suggest that mGlu receptors are necessary for sensitization to amphetamine (Kim & Vezina, 1998); however, the specific subtype(s) remain to be determined unequivocally. The present data suggest the mGlu5 receptor is a necessary component in the signalling cascade following cocaine administration that results in enhanced AMPA/NMDA receptor EPSC amplitude at excitatory synapses of VTA dopamine neurons. These findings therefore provide a potential cellular mechanism, apparently linking mGlu5 receptor function with the propensity to self-administer drugs of abuse.

Several forms of synaptic plasticity are dependent upon modulation of AMPA receptor trafficking to the cell surface. For example, NMDA receptor-dependent LTP is associated with recruitment of AMPA receptors to the cell surface (Collingridge et al. 2004). Indeed, group I mGlu receptors have been implicated in the trafficking of AMPA GluR2 subunits in the VTA (Mameli et al. 2007). Here we show that the basal AMPA/NMDA receptor EPSC amplitude ratio in mGlu5-deficient mice is lower than that observed in wild-type littersmates. This would be consistent with a reduced AMPA receptor number and/or function within the VTA of mGlu5-deficient mice compared to wild-type littermates. Furthermore, a relative inability to traffic relevant AMPA receptor subunits to the neuronal membrane would also be consistent with the lack of plasticity following cocaine challenge in mutant mice. Whether this is the case or not remains to be established; however, that does not detract from our striking observation that following a single dose of cocaine, mice devoid of mGlu5 receptors fail to show synaptic plasticity within the VTA. Indeed, the current data provide a parallel with the phenotype of mice lacking the GluR1 subunit of the AMPA receptor (Dong et al. 2004).

mGlu5-deficient mice were hyperactive compared to wild-type littersmates upon exposure to a novel environment, although this effect was abolished by subsequent re-exposure. A correlation between acute cocaine-induced locomotor activity and an increase in AMPA/NMDA receptor EPSC amplitude ratio has been observed previously, a phenomenon that was lost as rats became sensitized to the drug (Borgland et al. 2004). The delay in the onset of hyperactivity following acute cocaine in mGlu5-deficient mice may in theory reflect stereotypy that then gives way to hyperactivity. However, this explanation is unlikely because (i) the same behavioural profile to acute cocaine occurs at both 20 mg/kg (acute data) and 10 mg/kg (challenge day, saline/cocaine group); (ii) on days 2–5 of cocaine pre-treatment during the development of sensitization, the temporal profile of the response to cocaine in mutant mice matches that of wild-type mice (not shown) and (iii) sensitized mutant mice exhibit the same temporal profile as wild-types upon cocaine challenge (i.e. immediate peak followed by decay), rather than evidence of enhanced stereotypy. It is possible that the lower basal AMPA/NMDA EPSC amplitude ratio observed in the mGlu5-deficient mice in the present study may account for the different temporal profile in locomotor behaviour in response to acute cocaine administration. Furthermore, the subsequent ‘normalization’ observed in response to sensitized cocaine challenge would be consistent with the lack of correlation between VTA AMPA/NMDA receptor EPSC amplitude ratios and sensitized behaviour (Borgland et al. 2004). Indeed, locomotor sensitization has been linked to drug-induced plasticity onto medium spiny neurons in the accumbens shell (Thomas et al. 2001), and plasticity at corticostriatal synapses is attenuated in mice lacking mGlu5 receptors (Gubellini et al. 2003). There is, however, one important caveat, in that slice recordings were taken from mice somewhat younger than those employed for behavioural observations. Accordingly, it is possible that the differences between genotypes in terms of cocaine-induced synaptic plasticity may in part reflect a developmental difference.

mGlu5-deficient mice re-exposed to the drug-paired environment (cocaine/saline group) also exhibited a marked hyperactivity compared to control (saline/saline) counterparts, precluding the possibility that mutant mice have simply ‘forgotten’ the environment and are therefore hyperactive. Notably, this difference was not observed between the equivalent wild-type mice groups. Accordingly, these data suggest that the contextual component of the sensitized response is augmented in mGlu5-deficient mice. Thus, as there is no overall difference between genotypes in the sensitized response to cocaine, the contribution of drug-induced plasticity compared to context-induced behaviour in mGlu5-deficient mice would appear to be considerably less than in wild-type littermates. Furthermore, this dissection of the individual components that contribute towards a gross overall measure demonstrates the importance of robust controls for
context. While the sensitized response to cocaine between wild-type and mGlu5-deficient mice appears comparable on the surface, the underlying mechanisms are seemingly different.

In summary, the ability of a single dose of cocaine to alter the NMDA/AMPA receptor EPSC amplitude ratio in VTA dopaminergic cells is absent in mGlu5-deficient mice. While mGlu5-deficient mice show a differential locomotor profile to an acute cocaine challenge, they still develop and express sensitization to cocaine. This would argue for dissociation between drug-induced LTP-like plasticity at excitatory synapses of VTA dopamine cells and behavioural sensitization to cocaine in mice.

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Statement of Interest

None.

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