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Group I mGlu receptor modulation of dopamine release in the rat striatum in vivo

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Abstract

The present study investigated the ability of mGlu (metabotropic glutamate) receptor to modulate dopamine release in the striatum of freely moving rats assessed using the microdialysis technique. The group I and II mGlu receptor agonist (1*S*,3*R*)-ACPD (1-amino-cyclopentane-1,3-dicarboxylate; 1–3 mM) increased dopamine release (367% of basal levels) which was prevented by the non-selective mGlu receptor antagonist, (+)-MCPG (alpha-methyl-4-carboxyphenylglycine; 10 mM). The group I mGlu receptor agonist, DHPG (3,5-dihydroxyphenylglycine; 0.3–1 mM), also increased dopamine release (maximum increase 229%) which was also antagonised by (+)-MCPG (10 mM). In contrast, the group II mGlu receptor agonist, DCG-IV (2-(2,3-dicarboxycyclopropyl)glycine; 3–50 μM), induced a more modest increase in dopamine release (156% of basal levels). Combined administration of DHPG (1 mM) and DCG-IV (50 μM) maximally increased dopamine release by 252% of basal levels which was antagonised completely by (+)-MCPG (10 mM). Such findings indicate that group I (and possibly group II) mGlu receptors facilitate rat striatal dopamine release in vivo.

Keywords: mGlu receptor, Group I; mGlu receptor, Group II; Dopamine release; Striatum, rat; Microdialysis, in vivo

1. Introduction

The mGlu (metabotropic glutamate) receptors comprise a family ($mGlu_1$–$mGlu_8$ plus a number of alternatively spliced variants; e.g., see Pin and Duvoisin, 1995) which share a number of characteristics (e.g., sequence homology, relatively large extracellular N-terminal domain) which distinguishes them from other G-protein coupled receptors. Furthermore, mainly on the basis of their primary structure and associated transduction mechanisms in artificial expression systems, but also to some extent on their pharmacology, the eight mGlu receptors can be allocated to one of three groups; $mGlu_1$ and $mGlu_5$ receptors belonging to group I, $mGlu_2$ and $mGlu_3$ receptors belonging to group II and $mGlu_4$ and $mGlu_{6-8}$ make up group III. With respect to the associated transduction systems, heterologously expressed group I mGlu receptors activate phospholipase C whereas group II and III mGlu receptors are negatively coupled to adenylate cyclase (e.g., see Pin and Duvoisin, 1995; Conn and Pin, 1997). However, with respect to the transduction systems associated with native mGlu receptors, this categorisation is likely to be an oversimplification (e.g., see Pin and Bockaert, 1995).

An increasing number of central actions mediated via mGlu receptors have been reported which indicate that the pharmacological manipulation of mGlu receptors may provide therapeutic benefit (e.g., for reviews see Nicoletti et al., 1996; Conn and Pin, 1997); although the precise mGlu receptor subtype has often been not identified due to the paucity of subtype selective ligands. In the light of mGlu receptors representing a potential novel target to alleviate the symptoms of Parkinson's disease (for review see Nicoletti et al., 1996), it is of interest that mGlu receptors mediate animal behaviour indicative of an increase in dopamine release in the striatum (Sacaan et al., 1991, 1992; Kaatz and Albin, 1995; Feeley Kearney et al., 1997). The purpose of the present study was, therefore, to investigate directly whether mGlu receptors mediate an increase in dopamine release in the rat striatum and attempt to classify the mGlu receptors mediating the response. Preliminary reports of the data have been presented to the British Pharmacological Society (Bruton et al., 1996a,b).

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2. Materials and methods

2.1. Animal housing

Female Wistar rats (150–250 g; Charles River), were housed in groups of four in a controlled environment; temperature 21 ± 1°C, 40–50% humidity, under a 12 h light/dark cycle (lights on 0700–1900 h) and were given free access to food (high grade maintenance diet, SDS) and water.

2.2. Stereotaxic implantation of chronic indwelling guide cannulae for microdialysis studies

Rats were anaesthetised with ketamine (60 mg/kg, i.p.) and medetomidine (250 μg/kg, i.p.) before 5 mm chronically indwelling guide cannulae (19-gauge stainless steel tubing) were inserted stereotaxically (the tip of the indwelling guide cannulae were in the cerebral cortex overlying the striatum; final microdialysis probe tip location, A +0.2, V −7.5, L −2.5 relative to the bregma; Paxinos and Watson, 1986) and secured to the skull with screws and dental cement. The guide cannulae were kept patent with stylets. Post-operatively, the animals were removed from the frame and placed singularly in a heated (37°C) recovery cage and administered with buprenorphine (0.03 mg/kg subcutaneously s.c.) for post-operative analgesia and Baytril™ 2.5% (0.1 ml s.c.), a broad spectrum antimicrobial and bactericidal agent. An hour after the animals had been anaesthetized, they were injected with atipamazole (1 mg/kg s.c.), an α_2-adrenoreceptor antagonist to reverse the effects of the medetomidine. Any animal displaying circling behaviour after the operation was given diazepam (0.25 mg/animal i.p.). Immediately after the operation, the animals had free access to the oral rehydration agent, Lectade, and jelly (Sainsburys) before resuming their ordinary diet the following morning.

2.3. Assessment of dopamine release in the rat striatum using the in vivo microdialysis technique

At least 7 days after stereotaxic location of the guide cannulae, rats were placed in a single animal test cage (with free access to food and water) for approximately 12 h before being immobilised using a soft-cloth wrapping technique and the microdialysis probe (4 mm AN69 dialysis membrane, external/internal diameter 310/220 μm, molecular weight cut off 40,000; Hospal Medical; for probe construction see Barnes et al., 1992) was gently implanted into the striatum and secured with cyanoacrylate adhesive (Permabond C2). After at least an hour, the microdialysis probe was perfused with artificial cerebrospinal fluid (aCSF; mM: NaCl 126.6, KCl 2.4, KH_2PO_4 0.49, $MgCl_2$ 1.28, $CaCl_2$ 1.1, $NaHCO_3$ 27.4, Na_2HPO_4 0.48, glucose 7.1, pH 7.4) at 2 μl/min. Dialysate samples collected for at least the first 100 min were discarded and subsequent samples were collected every 20 min. After the establishment of a reproducible baseline of dialysate dopamine levels, drugs (or vehicle) were administered via the perfusing aCSF by using a liquid switch.

At the end of the experiment, the microdialysis probe placement was verified visually by coronal slicing of the brain using a freezing microtome. Data from animals where the microdialysis probes were not correctly located within the striatum were not included in the present report.

2.4. Quantification of dopamine by high performance liquid chromatography with electrochemical detection (HPLC-ECD)

Dialysate dopamine levels were quantified immediately after collection by HPLC-ECD. The HPLC-ECD system comprised of an isocratic pump (Gynkotek 300) which was connected to an analytical column (Hypersil 5 ODS:150 × 4.6 mm^2, HPLC Technology) via a Rheodyne injector. The eluate from the analytical column was passed into an electrochemical detector (Antec VT-03, Antec Analytical Technology; glassy carbon working electrode set at +0.7 V vs. Ag/AgCl reference electrode). The output from the electrode was monitored using a recording/plotting integrator (MacIntegrator). The HPLC-ECD system, with the exception of the integrator, was maintained at a constant temperature of 4°C inside a glass-fronted cool cabinet. The optimised mobile phase (methanol 15% v/v, NaH_2PO_4 0.12 M, octane sulphonic acid 0.45 mM, EDTA 0.1 mM, tetraethylammonium bromide 0.2 mM; pH 5.4, slight adjustments to the pH, methanol concentration and/or octane sulphonic acid concentration were made to overcome column to column variation) was delivered to the analytical column at a rate of 1.0 ml/min. The dopamine peak was identified and quantified by comparison with a known quantity of exogenous dopamine.

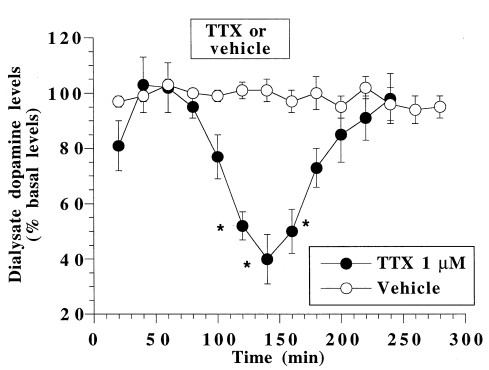

Fig. 1. Ability of the sodium channel blocker, tetrodotoxin (●; 1 μM; TTX), or vehicle (○; aCSF) to modulate striatal dopamine release in vivo, estimated by the microdialysis technique. Bar represents application of tetrodotoxin or vehicle via the microdialysis perfusate (corrected for void volume). Data represents the mean ± S.E.M., $n = 3–5$. $P < 0.05$ ANOVA, $^*P < 0.05$ Mann–Whitney U-test.

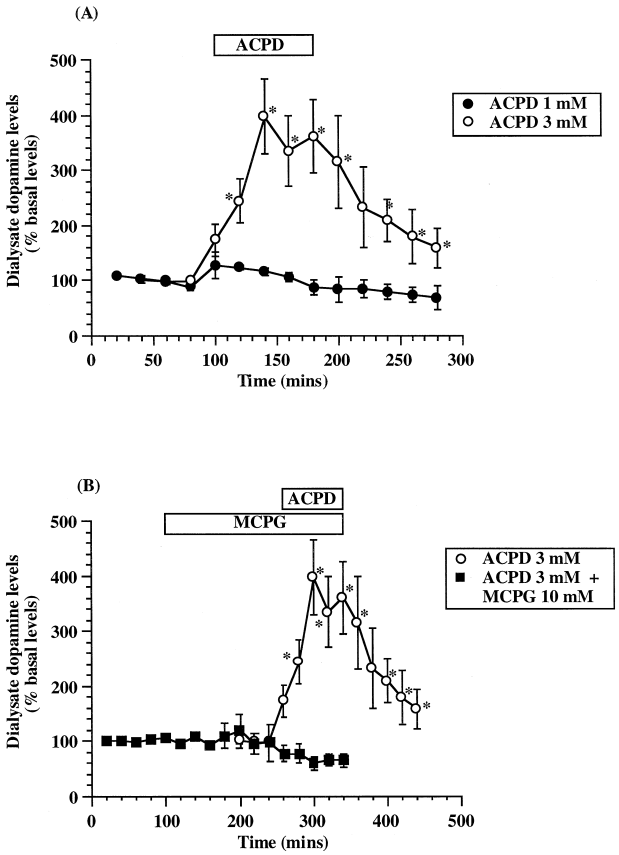

Fig. 2. Ability of the group I and II mGlu receptor agonist (1*S*, 3*R*)-ACPD (1–3 mM; A) to modulate striatal dopamine release in vivo, estimated by the microdialysis technique, and antagonism of the response by the non-selective mGlu receptor antagonist (+)-MCPG (10 mM; B). Bars represent application of the indicated drug via the microdialysis perfusate (corrected for void volume). Data represents the mean ± S.E.M., $n = 3–5$. $P < 0.01$ ANOVA, $^{*}P < 0.05$ Mann–Whitney *U*-test.

2.5. Data analysis

The mean level of dopamine in the four samples prior to drug administration was determined and the results are expressed as a percentage of this basal level. The results from individual experiments were then meaned and these are the values ± standard error of the mean (S.E.M.). An analysis of variance (ANOVA) test was performed on the data to demonstrate an overall significant effect in response to application of a drug, subsequently a Mann–Whitney *U*-test was performed between the last basal value and each subsequent value.

2.6. Drugs

(1*S*,3*R*)-ACPD (1-amino-cyclopentane-1,3-dicarboxylate, Tocris Cookson), atipamazole (Antisedan™, SB Pharmaceuticals), Bartril™ (Bayer), buprenorphine (Temgesic™, Reckett and Coleman), DCG-IV (2-(2,3-dicarboxycyclopropyl)glycine, Tocris Cookson), DHPG (3,5-dihydroxyphenylglycine, Tocris Cookson), ketamine (Vetalar™, Parke-Davis), MCPG (alpha-methyl-4-carboxyphenylglycine, Tocris Cookson), medetomidine (Domitor™, SB Pharmaceuticals) and tetrodotoxin (Sigma) were all used as received and were freshly prepared according to the manufacturers' instructions immediately before use.

3. Results

3.1. Characterisation of striatal dopamine release in vivo estimated by microdialysis

The limit of detection for dopamine quantified by HPLC-ECD was routinely between 0.6 and 3.0 pg (signal-to-noise ratio 3:1; injection volume 40 μl).

Striatal dialysate levels varied from animal to animal. Dialysate dopamine levels were therefore normalised to basal levels to assess drug effect. Basal release averaged 3.4 ± 0.5 pg/20 min (mean ± S.E.M., $n = 40$) and was not modified by the switching of syringes to deliver a different supply of aCSF (Fig. 1). Perfusion of tetrodotoxin (1 μM; via the microdialysis probe) resulted in a $60 \pm 9\%$ (mean ± S.E.M., $n = 3$) maximal decrease in dialysate

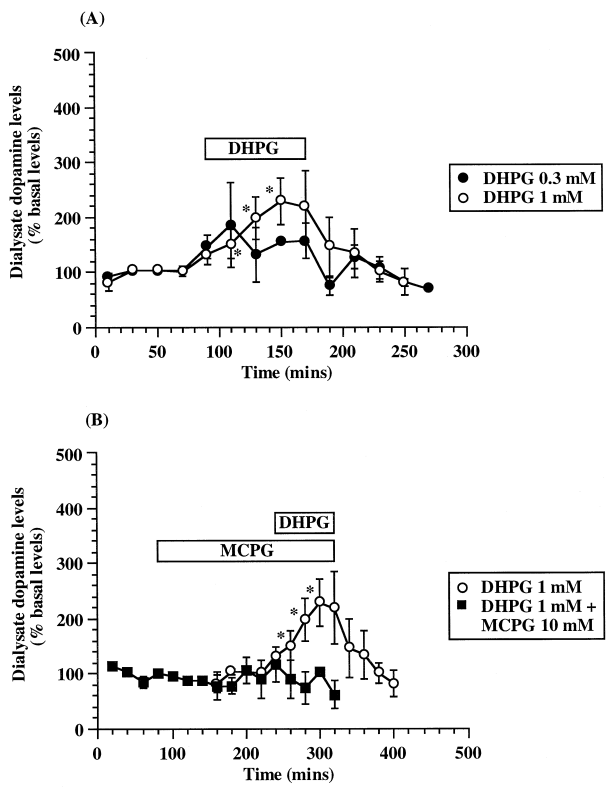

Fig. 3. Ability of the selective group I mGlu receptor agonist DHPG (0.3–1 mM; A) to modulate striatal dopamine release in vivo, estimated by the microdialysis technique, and antagonism of the response by the non-selective mGlu receptor antagonist (+)-MCPG (10 mM; B). Bars represent application of the indicated drug via the microdialysis perfusate (corrected for void volume). Data represents the mean ± S.E.M., $n = 3–5$. $P < 0.05$ ANOVA, $^{*}P < 0.05$ Mann–Whitney *U*-test.

dopamine levels which recovered to near basal after the removal of the tetrodotoxin (Fig. 1).

3.2. Ability of (1S,3R)-ACPD to modulate striatal dopamine release and antagonism by (+)-MCPG

Administration of the Group I and II mGlu receptor agonist (1*S*,3*R*)-ACPD (1–3 mM; delivered via the microdialysis probe) enhanced the dialysate levels of dopamine in a concentration-related manner (Fig. 2). The levels of dopamine in the dialysate samples reduced after perfusion of (1*S*,3*R*)-ACPD ceased, but did not return to basal levels during the remaining 100 min in which sampling continued. The non-selective mGlu receptor antagonist, (+)-MCPG (10 mM, administered via the microdialysis probe), failed to modify dialysate dopamine levels when administered alone although completely prevented the (1*S*,3*R*)-ACPD (3 mM, administered via the microdialysis probe)-induced elevation of dialysate dopamine levels (Fig. 2).

3.3. Ability of DHPG to modulate striatal dopamine release and antagonism by (+)-MCPG

Administration of the group I mGlu receptor agonist, DHPG (0.3–1 mM; via the microdialysis probe), increased the dialysate levels of dopamine in a concentration-related manner (Fig. 3). Dialysate dopamine levels returned to pre-drug levels 60 min after administration of the drug had ceased (Fig. 3). (+)-MCPG (10 mM; administered via the microdialysis probe) completely prevented the DHPG (1 mM; administered via the microdialysis probe)-induced elevation of dialysate dopamine levels (Fig. 3).

3.4. Ability of DCG-IV to modulate striatal dopamine release

DCG-IV, the group II mGlu receptor agonist (3–50 μM; administered via the microdialysis probe), induced a relatively modest increase in dialysate dopamine levels (Fig. 4) with dialysate dopamine levels returning to pre-drug levels some 40 min after administration of the drug had ceased (Fig. 4).

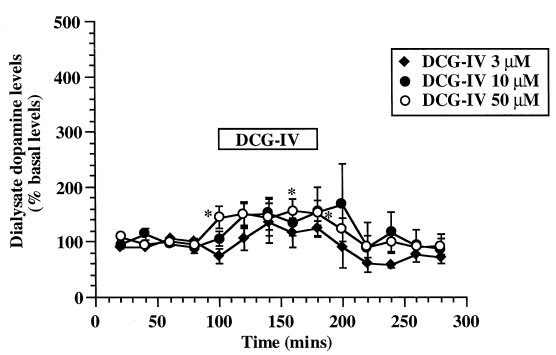

Fig. 4. Ability of the group II mGlu receptor agonist DCG-IV (3–50 μM) to modulate striatal dopamine release in vivo, estimated by the microdialysis technique. The bar represents application of DCG-IV via the microdialysis perfusate (corrected for void volume). Data represents the mean ± S.E.M., $n = 4$. $P < 0.05$ ANOVA, $^{*}P < 0.05$ Mann–Whitney *U*-test.

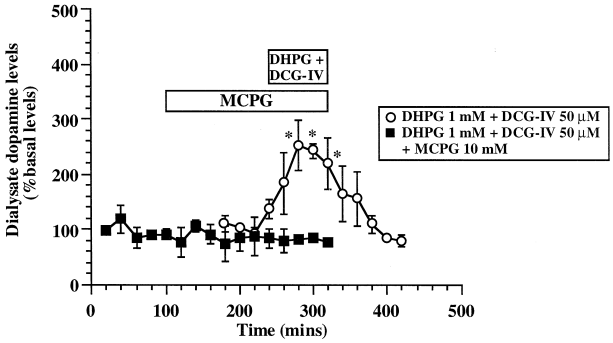

Fig. 5. Ability of the combined application of the group I mGlu receptor agonist DHPG (1 mM) and the group II mGlu receptor agonist DCG-IV (50 μM) to modulate striatal dopamine release in vivo, estimated by the microdialysis technique, and antagonism of the response by the non-selective mGlu receptor antagonist (+)-MCPG (10 mM). Bars represent application of the indicated drugs via the microdialysis perfusate (corrected for void volume). Data represents the mean ± S.E.M., $n = 3–4$. $P < 0.05$ ANOVA, $^{*}P < 0.05$ Mann–Whitney *U*-test.

3.5. Ability of DHPG in combination with DCG-IV to modulate striatal dopamine release and antagonism by (+)-MCPG

Combined administration of DHPG (group I mGlu receptor agonist, 1 mM) and DCG-IV (group II mGlu receptor agonist, 50 μM), via the microdialysis probe, increased dialysate dopamine levels (Fig. 5). Dialysate dopamine returned to basal levels 60 min after perfusion of the drugs had ceased. (+)-MCPG (10 mM; administered via the microdialysis probe) prevented completely the DHPG (1 mM) plus DCG-IV (50 μM; both administered via the microdialysis probe)-induced elevation of dialysate dopamine levels (Fig. 5).

3.6. Animal behaviour

None of the treatment regimens performed in the present study induced any overt behavioural change in the animal.

4. Discussion

The present studies utilised the microdialysis technique to estimate striatal dopamine release in freely moving rats and assess the ability of mGlu receptors to modulate this release. The basic methodology was identical to that we had used previously to demonstrate the ability of the 5-HT_4 receptor (5-hydroxytryptamine$_4$ receptor) and the AT_1 re-

ceptor (angiotensin AT_1 receptor) to modulate striatal dopamine release in the rat, in vivo (Brown et al., 1996; Steward et al., 1996). Consistent with these earlier reports, in the present study, dialysate dopamine levels appeared predominantly neuronal in origin since the majority of the dialysate dopamine was sensitive to the presence of the Na^+ channel blocker, tetrodotoxin (data not shown).

Our initial experiments demonstrated that the group I and II mGlu receptor agonist (1*S*,3*R*)-ACPD (Pin and Duvoisin, 1995) facilitated striatal dopamine release in a concentration-related manner and that the (1*S*,3*R*)-ACPD-induced response was antagonised by the non-selective mGlu receptor antagonist, (+)-MCPG (e.g., Hayashi et al., 1994; Bushell et al., 1996). The effective concentrations of the compounds (when the recovery from the microdialysis probe is taken into account; approximated to be 10%) and the overlapping pharmacology of (1*S*,3*R*)-ACPD and (+)-MCPG, indicates that the mGlu receptor mediating the response belongs to either the group I or II class of mGlu receptors (e.g., for reviews see Pin and Duvoisin, 1995; Conn and Pin, 1997). These results are similar to those reported previously assessing the action of (1*S*,3*R*)-ACPD to modulate dopamine release in the nucleus accumbens (Ohno and Watanabe, 1995; Taber and Fibiger, 1995).

Given the relatively non-selective action of (1*S*,3*R*)-ACPD, subsequent studies utilised more selective mGlu receptor agonists in an attempt to elucidate the individual roles of group I and group II mGlu receptors in the modulation of striatal dopamine release. DHPG, which is an agonist of the group I receptors (Schoepp et al., 1994), increased striatal dopamine release, although not with the same apparent efficacy as (1*S*,3*R*)-ACPD. Furthermore, the DHPG-induced increase in dopamine release was abolished by the combined presence of the mGlu receptor antagonist, (+)-MCPG, again indicative of a receptor-mediated response. It would therefore appear that activation of group I mGlu receptors at least contributed to the response-mediated by (1*S*,3*R*)-ACPD.

To assess the potential additional action of group II mGlu receptors in mediating the (1*S*,3*R*)-ACPD-induced increase in striatal dopamine release, the group II receptor agonist, DCG-IV (Hayashi et al., 1994), was utilised. DCG-IV evoked only a small increase in dopamine release, which was only significant at the highest concentration tested (50 μM; probably equivalent to approximately 5 μM in the tissue). Since tissue concentrations of approximately 1 μM should evoke near maximal group II receptor activation (e.g., for reviews see Pin and Duvoisin, 1995; Conn and Pin, 1997), the contribution of group II mGlu receptor activation to the (1*S*,3*R*)-ACPD-induced responses would appear to be at most minimal. In addition, given the known ability of DCG-IV to also activate NMDA receptors (Ishida et al., 1993), it remains a distinct possibility that this latter pharmacological action contributed to the DCG-IV-induced response. This is consistent with previous results indicating that NMDA receptor activation increases dopamine release in the striatum (e.g., Carrozza et al., 1992; Desce et al., 1992; Martìnez-Fong et al., 1992).

Despite the group I mGlu receptor agonist, DHPG, evoking a larger increase in striatal dopamine release compared to the group II mGlu receptor agonist, DCG-IV, the additional apparent efficacy of (1*S*,3*R*)-ACPD to increase dopamine release may have resulted from the combined activation of mGlu receptors from both group I and II. Indeed, Schoepp et al. (1996) have shown that (1*S*,3*R*)-ACPD-induced increases in cAMP formation in the neonatal rat hippocampus are mediated by a synergistic interaction between group I and group II mGlu receptors. We, therefore, postulated that there may be a similar synergistic relationship between the group I and group II mGlu receptors to facilitate dopamine release in the rat striatum and this action was responsible for the relatively high level of apparent efficacy displayed by the group I and II mGlu receptor agonist, (1*S*,3*R*)-ACPD. However, combined application of the group I agonist, DHPG (1 mM), and the group II agonist, DCG-IV (50 μM), failed to display a synergistic action to facilitate dopamine release. Indeed, the response to the combined administration of the agonists was below additive. However, since the response following combined application of these drugs was prevented completely by (+)-MCPG, this suggests that their actions were principally mediated via mGlu receptors. Other potential explanations concerning the different apparent efficacies of (1*S*,3*R*)-ACPD and DHPG to increase dopamine release, apart from potency/efficacy differences at native receptors, may relate to potential differences in their diffusion rates in the tissue.

While the present study has demonstrated that group I (and possibly group II) mGlu receptor activation increases dopamine release in the rat striatum, it would be difficult to define precisely which subtype or subtypes of mGlu receptors are mediating the response because the pharmacological tools with sufficient selectivity to allow discrimination between individual native mGlu receptor subtypes within a group are not available. For instance, discriminating between the mGlu receptors comprising group I, namely $mGlu_1$ and $mGlu_5$ receptors, relies on relatively small differences in the affinities of particular ligands (e.g., Brabet et al., 1995; Kingston et al., 1995), although a recent report describes the pharmacology of CHPG, which displays selectivity for the $mGlu_{5a}$ receptor vs. the $mGlu_{1a}$ receptor (Doherty et al., 1997). However, this ligand would appear to be a partial agonist and given that its selectivity was determined using heterologous expression of the receptors, the potency ratio and efficacy of the ligand at native mGlu receptors, where the level of expression is likely to be considerably lower, would be difficult to predict (Doherty et al., 1997). This limitation is enhanced by the difficulty to predict the precise tissue concentration of ligands in microdialysis studies and hence, the effects of CHPG were not assessed in the present study.

With respect to the cellular location of striatal mGlu receptors modulating striatal dopamine release, it is not known whether these receptors are expressed on dopaminergic terminals or whether the response involves an intermediate neurotransmitter system. Indeed, evidence is available to suggest that the mGlu receptor evoked increase in striatal dopamine release is a multi-synaptic mediated response. For instance, (1*S*,3*R*)-ACPD does not appear to modulate dopamine release from rat striatal slices (Sacaan et al., 1992) and subthalamic nucleus ablation abolishes the unilateral intra-striatal (1*S*,3*R*)-ACPD-induced, dopamine-mediated, rotational behaviour (Kaatz and Albin, 1995). A subsequent study by Albin's group, assessing FOS expression and [^{14}C]2-deoxyglucose utilisation, further implicated a role for the subthalamic nucleus in the mediation of the rotation induced by striatal mGlu receptor activation (Feeley Kearney et al., 1997). This latter group also concluded that the dopamine-mediated rotation was elicited by activation of group I mGlu receptors in the striatum, which, via multiple synaptic events, gives rise to striatal dopamine release. It should be noted, however, that while $mGlu_{1a}$ receptors do not appear to be expressed by nigro-striatal dopaminergic neurons (Testa et al., 1998), preliminary data indicates that at least one splice variant of a group I mGlu receptor, the $mGlu_{1d}$ receptor, is expressed by nigro-striatal dopaminergic neurons (Kosinski et al., 1997) and therefore, a direct interaction may (also?) be apparent. Indeed, the group I mGlu receptor agonists (1*S*,3*R*)-ACPD and DHPG directly activate dopaminergic neurons in the substantia nigra compacta (Mercuri et al., 1993; Wigmore and Lacey, 1998).

mGlu receptors have been forwarded as novel targets to alleviate the symptoms of Parkinson's disease. Thus, mGlu receptor ligands modulate the activity of glutamatergic subthalamic nucleus afferents (Kaatz and Albin, 1995; Abbott et al., 1997), which are believed to be overactive in Parkinson's disease (e.g., DeLong, 1990; Limousin et al., 1995). It has been hypothesised that the suppression of this overactive pathway would have at least two potential benefits. The first would be a reduction in the pathological overstimulation of GABA (gamma amino butyric acid)-ergic neurons in the internal pallidal segment, which would subsequently relieve the inhibition of motor activity (for review see Nicoletti et al., 1996). The second would be a reduction in the overactive glutamatergic stimulation of dopamine neurons in the substantia nigra compacta, which may contribute to the underlying excitotoxic loss of these neurons (Piallat et al., 1996; for review see Nicoletti et al., 1996), which represents the principal neurodegeneration associated with Parkinson's disease (e.g., for review see Javoy-Agid and Agid, 1990). The corollary of these studies suggests that mGlu receptor antagonists, specifically of group I or II mGlu receptors, may be useful in the treatment of Parkinson's disease. However, the present study has demonstrated that mGlu group I receptor agonists mediate an increase in striatal dopamine release and hence, group I mGlu receptor antagonists may further reduce striatal dopamine function in patients with Parkinson's disease. However, in the present study, the failure of the non-selective mGlu receptor antagonist, (+)-MCPG, to alter striatal dopamine release suggests that the endogenous tone on the mGlu receptor(s) modulating dopamine release is low and therefore, provided a similar low level of tone is apparent in the disease state, any benefit derived from antagonising group I mGlu receptors may not be compromised by a further reduction in striatal dopamine function. Hence, it would be of interest to test the behavioural effects of mGlu receptor ligands in an 'experimental' situation in which the nigro-striatal dopamine pathway had been decreased (e.g., following partial lesion with 6-OH-dopamine).

In summary, the present study has demonstrated that mGlu receptors modulate dopamine release in the rat striatum in vivo. The mGlu receptors responsible for the response belong to the group I class although an additional contribution of group II mGlu receptors remains a possibility.

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