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Sustained Behavioral Stimulation Following Selective Activation of Group I Metabotropic Glutamate Receptors in Rat Striatum

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WANG, J. Q. AND L. MAO. *Sustained behavioral stimulation following selective activation of group I metabotropic glutamate receptors in rat striatum.* PHARMACOL BIOCHEM BEHAV **65**(3) 439–447, 2000.—Group I metabotropic glutamate receptors (mGluRs) are densely expressed in the medium-sized spiny projection neurons of striatum. Activation of this group of the mGluRs modifies neuronal physiology through stimulation of phosphoinositide hydrolysis and intracellular Ca^{2+} release. Unlike the ionotropic glutamate receptors that mediate rapid synaptic transmission, activation of the mGluRs produces long-lasting actions brought about by modulation of activities of intracellular effectors. In this study, the role of the group I mGluRs in the modulation of extrapyramidal motor function was examined using a group I selective agonist, 3,5-dihydroxyphenylglycine (DHPG), in chronically cannulated rats. Bilateral injections of DHPG at a series of subtoxic doses (20, 40, 80, and 160 nmol) into the central part of the dorsal striatum produced hyperlocomotion and a unique stereotypical behavior (spontaneous and repetitive twitching movement of the head and forepaws) in a dose-dependent manner. The characteristic twitchy behavior usually commenced 30 min to 1 h, and could last as long as 10 to 12 h, after a single injection of the group I agonist. The behavioral responses to DHPG administration were markedly antagonized by intrastriatal injection of the group I antagonist PHCCC (10 nmol), but not the group II/III antagonist MSOPPE (10 nmol). Intrastriatal administration of 20 nmol dantrolene, an inhibitor of intracellular Ca^{2+} mobilization, also prevented DHPG-stimulated motor activities. However, blockade of dopamine D_1 receptors with systemic administration of SCH-23390 (0.1 mg/kg, SC) did not alter the ability of DHPG to provoke behavioral activities. These data indicate that selective activation of the DHPG-sensitive group I mGluRs in the striatum can produce long-lasting stimulation of motor activity. DHPG-induced motor stimulation involves the mobilization of intracellular Ca^{2+} stores, but appears to be independent of D_1 dopaminergic transmission. © 2000 Elsevier Science Inc.

Basal ganglia Motor activity Metabotropic glutamate receptor Dopamine NMDA DHPG PHCCC MSOPPE Dantrolene

EXCITATORY amino acids are major excitatory neurotransmitters in the CNS, which regulate a variety of neuronal activities through interacting with excitatory amino acid receptors. Excitatory amino acid receptors are divided into ionotropic (NMDA, kainate, and AMPA) or metabotropic (G-protein coupled) receptors according to their biochemical, pharmacological, and molecular profiles (38). Compared to thoroughly investigated roles of the ionotropic receptors in the regulation of cellular activity, functional studies on metabotropic glutamate receptors (mGluRs) are just emerging in the recent years (76,81). At present, eight subtypes of mGluRs (mGluR1–8) have been cloned in tissues from rat brain. Like the ionotropic receptors, these subtypes are heterogeneous in their distribution, pharmacology, and linkages to intracellular second messenger systems (25,39,51,53). Based on intracellular responses to activation of a specific subtype of the mGluRs expressed in *Xenopus* oocytes, the eight subtypes of the mGluRs are classified into three major functional groups. Activation of the group I mGluRs (mGluR1 and mGluR5) increases turnover of phosphoinositide hydrolysis, which gives rise to two products, diacylglycerol and 1,4,5-triphosphate. The latter can substantially increase intracellu-

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lar Ca^{2+} concentration by releasing Ca^{2+} from intracellular Ca^{2+} stores to cytoplasm (5,37). Activation of the group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7 and mGluR8) mGluRs, on the other hand, reduces cAMP formation by inhibiting adenylate cyclase activity (44,47). Thus, mGluRs, via their linkages to diverse intracellular effectors, may exert a strong influence on intracellular activities related to long-term changes in cellular physiology, as opposed to the ionotropic receptors, which are ligand-gated cation channels and typically process rapid synaptic transmission.

Abundant glutamatergic terminals project from widespread areas of forebrain (cerebral cortex, thalamus, amygdala, hippocampus, and prefrontal cortex) to the striatum (34,35), a central structure of the basal ganglia controlling extrapyramidal movement. A large proportion of extrinsic glutamatergic terminals make asymmetrical (excitatory) synaptic contact with the striatal neurons, mainly medium-sized spiny projection neurons (12,17,59,60). Parallel with the ample glutamatergic innervation, mGluRs that glutamate interacts with are densely distributed in striatal neurons according to a large number of the recent morphological studies. For instance, high levels of mGluR binding sites exist in the striatal region (1). A lesion of the corticostriatal projections had minimal effect on the striatal mGluR binding quantity, indicating that the majority of mGluRs are located on postsynaptic neurons (83). The studies with in situ hybridization (26,40,56,63–65) and immunocytochemistry (16,31,57) show the presence of mGluR mRNAs and proteins in striatal neurons, respectively, with mGluR3 and mGluR5 at high, and mGluR1 and mGluR4 at low to moderate, levels (65). Given the anatomically concentrated presence of mGluR-mediated glutamatergic transmission in the striatum, one can speculated that mGluRs might be intimately involved in the modulation of overall striatal functions.

Initial functional studies demonstrate the participation of striatal mGluRs in extrapyramidal motor modulation (70). Schoepp's group (48,49) first reported that a unilateral injection of a nonsubgroup selective mGluR agonist, 1S,3R-ACPD, into the dorsal striatum in anesthetized rats caused turning behavior (rotation) contralateral to the injection side 3–5 h after the drug injection when animals recovered from anesthesia. These findings have generally been replicated afterwards by others (14,15,24,58). Because the locomotor responses to 1S,3R-ACPD were blocked by an mGluR antagonist, but not by an ionotropic receptor antagonist, selective activation of mGluRs are likely to mediate the mGluR agonist-stimulated behavior (15,58). As to the mGluR subgroup(s) responsible for the mediation of behavioral stimulation, the group I mGluR agonist, 3,5-dihydroxyphenylglycine (DHPG) (22,54), was found to be more potent than 1S,3R-ACPD in terms of producing contraversive turning, whereas a group II or a group III agonist induced no rotation (15) or sedation (29). Moreover, rotations induced by DHPG or 1S,3R-ACPD were sensitive to a group I antagonist, but not to a group II/III antagonist (15). Apparently, activation of the group I mGluRs mediates the turning behavior induced by the mGluR agonists.

To further characterize the role of the group I mGluRs in the regulation of extrapyramidal motor activity, behavioral responses to selective activation of striatal group I mGluRs with DHPG were investigated in the rats in this study. Instead of testing circling behavior in the acutely prepared animal model used in the most previous studies (14,15,43,44), a chronically cannulated rat model was employed in this study. In this model, bilateral injections of DHPG into the central part of the dorsal striatum (caudoputamen) were made in conscious rats 5–7 days from surgery, and overall behavioral responses were monitored after the drug administration.

METHOD

Animals

Adult male Wistar rats (225–249 g, Charles River, NY) were individually housed and maintained on a 12 L:12 D schedule, with food and water provided ad lib. All animal use procedures were in strict accordance with the NIH Guide for the Care and Use of Laboratory Animals, and were approved by the Institutional Animal Care and Use Committee.

Drug Administration

Rats were anesthetized with 4% chloral hydrate (400 mg/kg, IP) and placed in a David Kopf stereotaxic holder. Two 24-gauge stainless steel guide cannulas (10 mm in length) were bilaterally implanted to the central part of the dorsal striatum (1 mm anterior to bregma, 2.5 mm lateral to midline, and 3 mm below surface of skull) or the nucleus accumbens (1 mm anterior to bregma, 0.7–1.2 mm lateral to midline, and 5 mm below surface of skull). The guide cannula was sealed with a stainless steel wire of the same length (10 mm). Rats were allowed at least 5 days for recovery from surgery. On the day of the experiment, the inner steel wire was replaced by a 30-gauge stainless steel injection cannula with a length of 12.5 mm that protruded 2.5 mm beyond the guide cannula. Through the injection cannula, drugs were infused into the target area at a rate of 0.4 μl/min in freely moving animals in the quiet (low stress) home cage. We selected 1 μl as the injection volume because no difference in potency of DHPG in stimulating behavior was found among the different injection volumes (0.5, 1, and 2 μl) that contain the same dose of the drug. Progress of injection was monitored by observing movement of a small air bubble through a length of precalibrated PE-10 tubing inserted between the injection cannula and a 5-μl Hamilton microsyringe. After completing each injection, the cannula was left in place for an additional 3 min to reduce any possible backflow of the solution along the injection track.

When effects of the mGluR antagonists or the Ca^{2+} release inhibitor on DHPG responses were examined, bilateral intrastriatal injections of these agents or their vehicle controls were given 10 min prior to DHPG administration. Subcutaneous injection of the dopamine D_1 receptor antagonist, SCH-23390, or saline in a volume of 0.8 ml/kg was made 20 min prior to the intrastriatal injection of DHPG.

Behavioral Observation

Behavioral activities in response to the drug treatments were continuously observed and rated in the animal's home cage. Two trained observers, blind to the drug treatments, rated the behavior of each rat at the designated time points. An eight-point rating scale (Table 1) modified from Ellinwood and Balster (13) was used to quantify behavioral changes in this study.

Experimental Protocols

A series of four experiments was conducted in this study. Experiment I characterized the effect of intrastriatal DHPG injection on spontaneous behavioral activity. Four different doses of DHPG (20, 40, 80, and 160 nmol/1 μl, corresponding to 3.7, 7.3, 14.7, and 29.3 μg/1 μl) were tested, and behavioral re-

TABLE 1

THE EIGHT-POINT SCALE MODIFIED FROM ELLINWOOD AND BALSTER (13) FOR QUANTITATION OF BEHAVIORAL ACTIVITIES IN RESPONSE TO INTRASTRIATAL DRUG TREATMENTS

Rate	Behavioral activity
1	Asleep, inactive
2	Normal activities (normal grooming, eating, drinking, and moving)
3	Increased activity
4	Hyperactive or fast movements (fast patterned walking, running, or jumping)
5	Slow patterned repetitive exploration and intermittent head/forepaw twitching
6	Fast patterned repetitive exploration and intermittent head/forepaw twitching
7	Stereotypy (repetitive head/forepaw twitching in one location to the exclusion of other activities)
8	Seizures

sponses to the drug treatments were observed in the course of 24 h. Experiment II evaluated specificity of the group I mGluRs in mediating DHPG-stimulated behaviors. Effects of the selective group I antagonist, n-phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide (PHCCC) (2), or the selective group II/III antagonist, (RS)-α-methylserine-O-phosphate monophenyl ester (MSOPPE) (67), on DHPG-stimulated behaviors were investigated in this study. Experiment III tested effects of inhibition of intracellular Ca^{2+} release with the inhibitor, 1-[[[5-(4-nitrophenyl)-2-furanyl]methylene]amino]-2,4-imidazolinedione (dantrolene), on the behavioral action of DHPG. To evaluate possibility that the mGluR agonist affected behavior indirectly through facilitating local release of dopamine, a major transmitter in this region well known to stimulate motor activity, the behavioral effect of DHPG was examined in Experiment IV under the condition of pharmacological blockade of dopamine D_1 receptors by pretreatment with the D_1 antagonist, (R)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (SCH-23390).

Histology

At the end of each experiment, 0.5 μl of 4% methylene blue dye was applied to the injection site. Animals were deeply anesthetized with 4% chloral hydrate (500 mg/kg, IP) and then decapitated. The brains were removed rapidly from skull and immediately frozen in isopentane at −40°C and stored at −70°C until they were sectioned for histological examination. Frozen serial sections (20 μm) of the forebrain were cut at the injection level and thaw mounted onto gelatin-coated slides. The sections were fixed, defatted, and stained for Nissl substance with 0.1% Thionin. Accurate injection sites and morphological structure of the tissue surrounding the injection site were checked by referring to the Paxinos and Watson Atlas (43). Locations of the blue spots in the dorsal striatum were plotted onto copies of standard sections of the striatum taken from the atlas. Only rats showing the appropriate injection sites were used for data analysis.

Drugs

All drugs were purchased from Tocris Cookson Inc. (Ballwin, MO), and freshly prepared on the day when intracranial injections were made. SCH-23390 and dantrolene were dissolved in physiological saline. DHPG was dissolved in physiological saline with moderate heating. PHCCC was dissolved in DMSO and diluted with saline. MSOPPE was dissolved in 50 mM NaOH and diluted with saline. Doses of the drugs were changed with altering concentration but not volume. Solutions of all drugs were neutralized to pH 7–8 with 1 N NaOH. The doses of SCH-23390 and dantrolene were calculated as the salt, whereas the doses of other drugs were referred to their free bases.

Statistics

The results are shown as mean ± SEM. Data were analyzed by a two-factor analysis of variance (ANOVA), followed by the Newman–Keuls a posteriori test for individual group mean comparisons, or by Student's paired or unpaired *t*-test, as appropriate. $p < 0.05$ was taken as significant level of difference.

RESULTS

Experiment I

Behavioral responses to injection of DHPG into the dorsal striatum. It was first observed that bilateral injections of DHPG at doses in the pmol range (10, 100, and 1000 pmol) did not cause a reliable change in behavior when tested in the three groups of rats (n = 3–4 per group, data not shown). DHPG was then tested at doses in the nmol range (0, 20, 40, 80, and 160 nmol) in the five other groups of animals (n = 4–5 per group). As can be seen from Fig. 1, a dose-dependent and prolonged change in behavioral activity occurred following intrastriatal injection of DHPG in this dose range. The lowest dose of DHPG (20 nmol) did not produce any detectable change in behavioral activity. At the middle dose (40 nmol), DHPG started to increase locomotion (face-washing, rearing, fast walking, and sniffing with moderate intensity). A statistically significant level was reached 45 min after the drug injection compared to the groups of rats given 20 nmol DHPG or saline. The increased locomotion could last approximately 6 h,

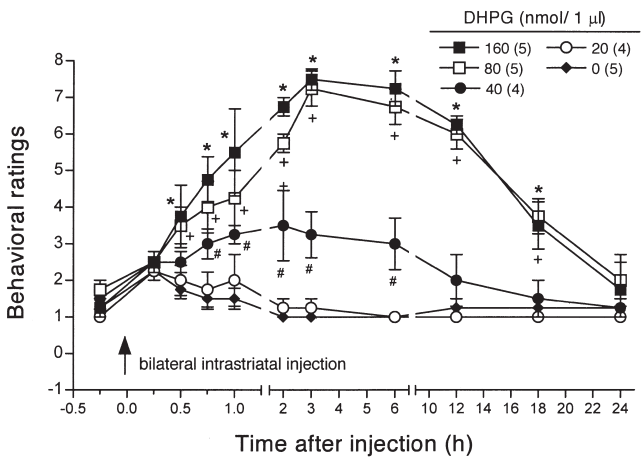

FIG. 1. Effect of microinjection of the group I mGluR agonist DHPG into the dorsal striatum on rat spontaneous behavioral activity. Delayed and remarkably prolonged changes in behavioral activation (locomotion and stereotypy) were produced by a single injection of DHPG. The values are expressed as mean ± SEM. The numbers in parentheses in the upper right legend represent number of animals tested. *,+,#$p < 0.05$ compared with vehicle group.

and returned to the baseline level within 12 h. Injection of DHPG at the two higher doses (80 and 160 nmol) virtually caused similar changes in behaviors in terms of intensity and duration. The hyperlocomotion was the same as that seen after 40 nmol, but with higher intensity. The hyperlocomotion then evolved into slow or fast pattered exploratory behavior with intermittent occurrence of a unique spontaneous behavior characterized by regular twitching movement of the head and forepaws with constant head up. At 2–3 h, behavioral repertoire was manifested by continuous and intensive head/forepaw twitching (stereotypical behavior), usually in one location of the cage, and exclusive all other activities. The characteristic twitches could last 10–22 h, with a little decrease in their intensity over the time. The stimulated behavioral activity turned back to the hyperlocomotion from the stereotypy 12–18 h after the drug injection. At 24 h, motor activity returned to the normal level. In addition, one animal received 160 nmol DHPG exhibited frank seizures, which took place approximately 2 h after drug injection and repetitively occurred for a half hour.

The behavioral activities induced by DHPG were reproducible. In four rats, injections of DHPG at the doses of 80 or 160 nmol (two per dose) were repeated 2 days after the initial experiments. The behaviors induced by second injection paralleled with that seen after the initial injection at the same doses (data not shown).

Injections of DHPG were made bilaterally to the nucleus accumbens (two for 160 nmol and seven for 80 nmol) in nine rats. Behavioral responses to these injections were distinguishable from that seen after drug injection into the dorsal striatum described above. Primarily, intraaccumbens injection of DHPG increased locomotor activity, which also underwent a long period of time (10–18 h). However, neither twitching nor any other form of stereotypies was seen following the drug injection into the nucleus accumbens.

Distributions of the injection sites in the dorsal and ventral striatum from the above experiments are illustrated in Fig. 2. The injection sites in the dorsal striatum were concentrated in the dorsal part of the caudoputamen. The injection sites in the nucleus accumbens were mainly distributed in the shell. In addition, morphological structure of neurons surrounding the cannula tracks of intrastriatal or intraaccumbens injection of DHPG was preserved, and showed no difference from that seen in control animals.

In a separate study, behavioral changes induced by bilateral administration of DHPG into the dorsal striatum were compared to that induced by a unilateral injection of the drug into the same part of the striatum. In this study, the dose of 80 nmol was selected from the above dose–response study in which injection of DHPG at this dose produced a maximal change in behavior. In the studies with unilateral injection, control saline was injected into one side while DHPG was injected into the another. According to the data illustrated in Fig. 3, the unilateral administration was apparently less potent than the bilateral injection for behavioral stimulation. Unilateral DHPG actually caused only hyperlocomotion. The stereotypical head/forepaw twitching was not induced by the unilateral injection. In addition, unilateral DHPG did not cause consistent and reliable rotation either contralateral or ipsilateral to the injection side.

Experiment II

Effects of the group I- and group II/III-specific antagonists on DHPG-stimulated behaviors. The dose of DHPG (80 nmol) that produced maximal behavioral responses was selected again in this experiment as well as in the following experiments III and IV. In the rats treated with vehicle + DHPG, the typical DHPG-like behaviors, i.e., an initial hyperlocomotion replaced by the prolonged head/forepaw twitching were seen (Fig. 4A). Pretreatment with the group I antagonist PH-

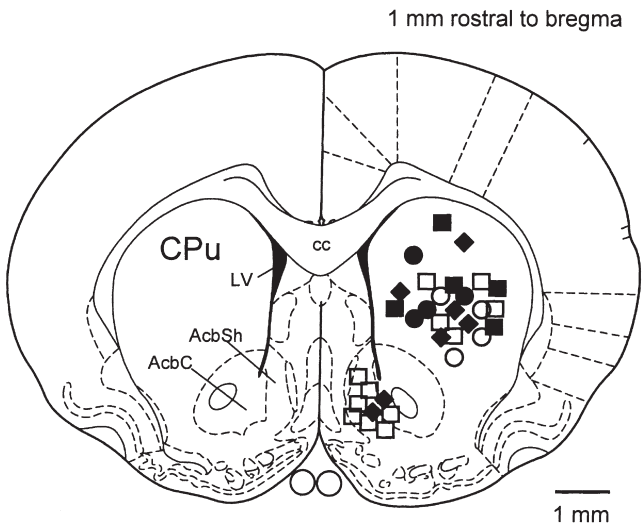

FIG. 2. Reconstruction of microinjection sites in the rat dorsal and ventral striatum in response to administration of the group I mGluR agonist DHPG. The injection sites were marked on one side of the striatum. Filled squares: 160 nmol; open squares: 80 nmol; filled circles: 40 nmol; open circles: 20 nmol; filled diamonds: vehicle. AcbC, core of nucleus accumbens; AcbSh, shell of nucleus accumbens; cc, corpus callosum; CPu, caudate putamen; LV, lateral ventricle (according to the atlas of Paxinos and Watson) (43).

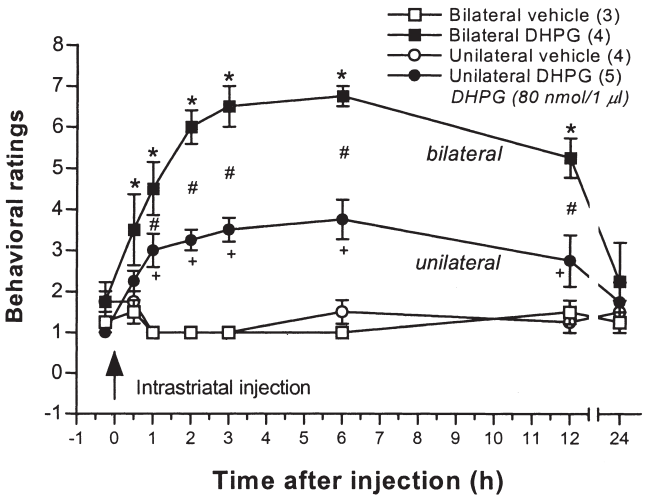

FIG. 3. Comparison of behavioral responses to bilateral and unilateral injection of the group I mGluR agonist DHPG into the dorsal striatum at a dose of 80 nmol. Hyperactivity induced by the bilateral administration of DHPG was approximately twice as strong than that produced by the unilateral administration of DHPG. The values are expressed as mean ± SEM. The numbers in parentheses in the upper right legend represent number of animals tested. *,+$p < 0.05$ compared with corresponding vehicle treatment. #$p < 0.05$ compared between bilateral and unilateral injection of DHPG.

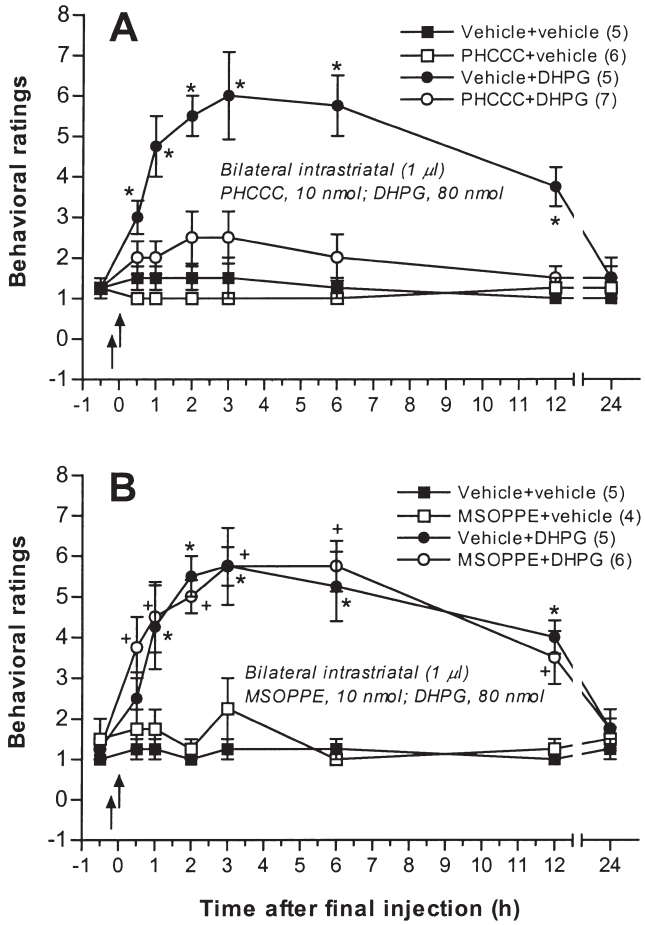

FIG. 4. Effects of blockade of group I (A) or group II/III (B) mGluRs on the DHPG-stimulated behaviors. Bilateral injections of the group I antagonist PHCCC (10 nmol) or the group II/III antagonist MSOPPE (10 nmol) were made 10 min prior to injection of DHPG (80 nmol). The behavioral responses to DHPG were blocked by PHCCC (A), but not by MSOPPE (B). Arrows from left to right, start of intrastriatal injections of the antagonists and the agonist. The values are expressed as mean ± SEM. The numbers in parentheses in the legend represent number of animals tested. *$p < 0.05$ for vehicle + DHPG vs. vehicle + vehicle. +$p < 0.05$ for MSOPPE + DHPG vs. vehicle + vehicle.

CCC (10 nmol) prevented these DHPG-stimulated behaviors (Fig. 4A). PHCCC by itself, however, did not modify spontaneous motor activity (Fig. 4A).

In contrast to the blocking effect of PHCCC, pretreatment with the group II/III antagonist MSOPPE (10 nmol) had no effect on the DHPG-stimulated behaviors (Fig. 4B). MSOPPE alone did not alter spontaneous motor activity (Fig. 4B).

Experiment III. Effect of the intracellular Ca^{2+} release inhibitor dantrolene on DHPG-stimulated behaviors. Behavioral responses to bilateral injections of dantrolene (20 nmol) + vehicle were not different from that observed from rats treated with vehicle + vehicle (Fig. 5). However, in the rats pretreated with dantrolene, 80 nmol DHPG no longer produced significant alteration in spontaneous motor activity for an entire 24-h period of observation (Fig. 5). In the absence of dantrolene, DHPG showed its ability to induce hyperlocomotion and twitchy stereotypy (Fig. 5).

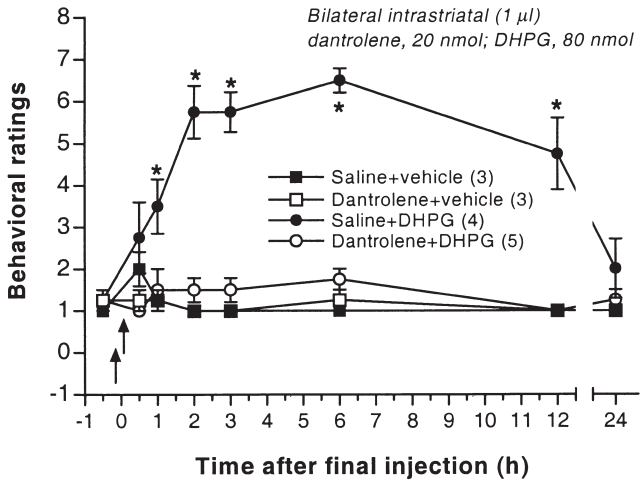

FIG. 5. Effect of inhibition of intracellular Ca^{2+} release on the DHPG-stimulated behaviors. Bilateral injections of the Ca^{2+} release inhibitor dantrolene (20 nmol) were made 10 min prior to injection of DHPG (80 nmol). The behavioral responses to DHPG were blocked by dantrolene. Arrows from left to right, start of intrastriatal injections of dantrolene and DHPG. The values are expressed as mean ± SEM. The numbers in parentheses in the legend represent number of animals tested. *$p < 0.05$ for vehicle + DHPG vs. vehicle + vehicle.

Experiment IV. Effect of the dopamine D_1 receptor antagonist SCH-23390 on DHPG-stimulated behaviors. Subcutaneous injection of SCH-23390 at a dose of 0.1 mg/kg moderately sedated rat activity. However, in the rats pretreated with SCH-23390, the behavioral responses to intrastriatal injection of DHPG (80 nmol) remained as strong as those observed in the rat given DHPG alone (Fig. 6). The time course and magni-

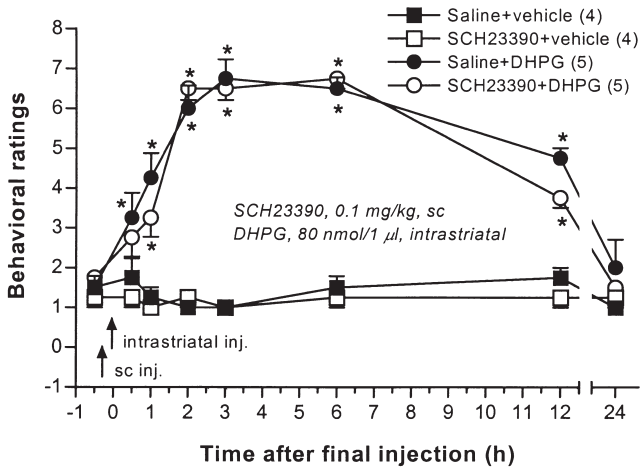

FIG. 6. Effect of blockade of dopamine D_1 receptors on the DHPG-stimulated behaviors. Systemic administration of the D_1 subtype-specific antagonist SCH-23390 (0.1 mg/kg, SC) was made 20 min prior to intrastriatal injection of DHPG (80 nmol). The behavioral responses to DHPG were not affected by pretreatment with SCH-23390. Arrows from left to right, start of systemic and intrastriatal injections. The values are expressed as mean ± SEM. The numbers in parentheses in the legend represent number of animals tested. *$p < 0.05$ compared with saline + vehicle.

tude of the behavioral changes induced by DHPG was not shifted by coadministration of SCH-23390.

DISCUSSION

A series of experiments was conducted in this study to characterize the role of the group I mGluRs in the striatum in motor modulation. We found that selective activation of the group I mGluRs with bilateral injections of the group I agonist DHPG into the dorsal striatum induced hyperactivity and a stereotypical behavior characterized by repetitive twitching movement of the head/forepaws. The behavioral responses were dose-dependent and maintained for a remarkably long period of time, more than 18 h after the injection. The motor stimulation was sensitive to a group I antagonist, but resistant to a group II/III antagonist, demonstrating specificity of the group I mGluRs in the mediation of the behavioral effect of DHPG. Inhibition of intracellular release of Ca^{2+}, the key transducer downstream to activation of the group I mGluR/phosphoinositide hydrolysis pathway, prevented DHPG-stimulated behaviors. Thus, Ca^{2+} mobilization is linked to action of the group I agonist. Finally, dopaminergic activity seems not important for the DHPG action because blockade of dopamine D_1 receptors did not modify DHPG-stimulated behaviors.

Motor stimulation (rotation) following a unilateral intracaudate injection of 1S,3R-ACPD was seen in a number of reports (14,15,48,49). Noticeably, these experiments were conducted in the acutely prepared and anesthetized rats. Intracaudate injection of the mGluR agonist was made when animals were under anesthetized state. Rotational behavior, therefore, had to be observed 3–5 h postinjection as the animals recovered from anesthesia. When the similar experiment was attempted in the animal model, in which chronic cannulation was made and 1S,3R-ACPD was injected into the dorsal striatum in conscious state 5–7 days after animals recovered from the cannulation surgery, behavioral responses were significantly different. The turning behavior was hardly seen following 1S,3R-ACPD injection (73,80). Similarly, turning behavior after unilateral injection of DHPG in anesthetized state (15) was not consistently seen in this study. Only in the nucleus accumbens, did injection of 1S,3R-ACPD cause rotation or locomotion in conscious rats (4,58). Reasons for the disparity were not clear. However, the difference in animal preparation could be decidedly important. With noninterference of anesthetics, the chronically implanted rat model is considered to be closer to normal physiological conditions. In addition, the difference in doses may also be responsible. The effective doses for unilateral DHPG to induce rotation range from 500–1000 nmol (15), which is higher than the ceiling doses of bilateral DHPG (80 and 160 nmol) established in this study to produce maximal motor stimulation.

Striking aspect of the DHPG action is the sustained motor stimulation following a single injection of the drug. The motor stimulation, which remained as long as 18 h, is far longer than the time frame of behavioral activity evoked by stimulation of many other transmitter systems surveyed so far. For instance, dopamine receptor agonists stimulate behavior for the duration of 1–4 h, depending upon doses administered (74,75,79). Anticholinergic treatment or blockade of $GABA_A$ receptors increase motor activity for 30 min to 3 h, probably through disinhibition of the striatonigral projection neurons (23,77, 78). Injection of NMDA or NMDA receptor agonists into the dorsal or ventral striatum causes all different kinds of responses (stimulation, depression, or no effect) (20,52,61). In the reports where stimulation of motor activity is exhibited, NMDA usually increases motor activity for 30 min to a few hours, depending on doses employed (6,11,18,42,66,68). Mechanism(s) underlying the long-term action of DHPG is unclear. It may be related to prolonged changes in certain intracellular metabotropic activity, such as sustained Ca^{2+} increase seen after DHPG application (45).

In a recent study, locomotion induced by 1S,3R-ACPD injected into the nucleus accumbens lasted only 30 min in chronically cannulated rats (4). If the stimulatory effect of 1S,3R-ACPD on behavior was mediated via stimulation of group I mGluRs, the short-lasting motor stimulation after group I mGluR activation with 1S,3R-ACPD is in sharp contrast to the long-lasting behavioral effect of DHPG. This seems to suggest that the long-lasting effect observed in this study is unique to DHPG, rather than to group I mGluR activation per se. However, as a nonselective agonist, 1S,3R-ACPD stimulates all groups of mGluRs concomitantly (21,55). The recent studies performed in this laboratory and others show that activation of group II/III mGluRs suppressed spontaneous motor activity (29) and basal dopamine release in the striatum (19). Thus, concomitant group II/III mGluR stimulation with 1S,3R-ACPD may limit excitatory behavioral responses to this drug. This may more or less contribute to the short pattern of behavioral stimulation in response to 1S,3R-ACPD administration.

In addition to the exceptional long-term effect, stereotypy, a behavior characterized by its lack of variability (13,46), induced by DHPG, is also unique. It has been well documented that dopamine stimulation induces stereotypy marked as repetitious sniffing and rearing in the same place of the cage (74,79). The typical components of stereotypies after excessive NMDA stimulation contain irregular choreiform movements of head and forepaws and barrel rolling (68). Characteristic head shaking and retraction were seen after intrastriatal administration of a 5-HT receptor agonist (10) or $GABA_A$ receptor antagonist (23). DHPG defines its stereotypy as spontaneous and regular twitching movement of head/forepaws with head constantly pointing up. Although detailed neurochemical mechanisms contributing to variation of these stereotypies are unclear, distinctive stereotypy may serve as a functional marker for effective pharmacological stimulation of a given receptor.

Seizures were seen in one rat treated with 160 nmol DHPG. The behavioral symptoms of these seizures are similar to "generalized seizures" described on human subjects. The repetitive and brief seizure attacks were accompanied by a transient loss of consciousness (absence seizure) and postural control. The rats fell to the ground and suffered tonic–clonic movements, i.e., periods of increased muscle tone (the tonic phase) alternating with periods consisting of jerky movements (the clonic phase). Apparently, the stereotypical twitching movements of the head and forepaws are different from these classic seizures, because rats remained conscious, and postural control and the twitches displayed continuously. However, the stereotypical behavior may reflect a behavioral stage that can be readily progressed to seizure attack.

1S,3R-ACPD was used as a selective mGluR agonist in the most of the early behavioral studies. Because it has a large spectrum agonist property on group I and II mGluRs (21,55), application of this agonist is not able to clarify subtype(s) responsible for the behavioral stimulation. Unilateral intrastriatal injection of the group I subtype-specific agonist DHPG induced contraversive turning as opposed to inability of a group II and a group III agonist to induce such a behavior (15). Bilaterally intrastriatal injections of DHPG induced hy-

perlocomotion and stereotypical behavior (this study). The behavioral activities induced by both unilateral and bilateral injection of DHPG were blocked by the group I, but not the group II/III, antagonist [(15); this study]. Thus, activation of the group I, but not the group II/III, mGluRs exerts a positive influence on behavioral activity. DHPG also increases phosphoinositide hydrolysis and intracellular Ca^{2+} level in the CNS neurons (9,72). Inhibition of intracellular Ca^{2+} release abolished the DHPG-stimulated behaviors (this study). Thus, the DHPG-sensitive group I mGluR–phosphoinositide hydrolysis–Ca^{2+} signal forms an intracellular cascade positively linked to the upregulation of striatal output and motor activity. As to relative importance of mGluR1 or mGlu5 subtype, pharmacological delineation will have to reply on future development of subtype-specific agonist/antagonist.

Precise pre- or postsynaptic mechanisms underlying the behavioral effects of the group I mGluR agonist are not well understood with limited studies so far performed in complex in vivo animal model. It is likely that exogenous administration of DHPG could directly stimulate the mGluRs postsynaptically located on medium spiny neurons. This consumption is based on the notion that the group I mGluRs are preferentially postsynaptic receptors in the striatum as opposed to the group II/III mGluRs preferentially being presynaptic receptors in the same region (81). In fact, 90% of mGluRs in the striatal region are located on intrinsic neurons (83), and a large proportion of extrinsic glutamatergic terminals make asymmetrical (excitatory) synaptic contact with postsynaptical striatal neurons (12,17,59,60). Additionally, 1S,3R-ACPD increases c-*fos* immediate early gene expression, a presumed indicator of neuronal activity, in dissociated striatal neurons in vitro (71). However, it should not be underestimated that the mGluR agonist could alternatively affect local release of transmitter(s) through interacting with presynaptically located auto- or heteroreceptors, which in turn, stimulates striatal neurons and, as a result, behavioral activity. Infusion of 1S,3R-ACPD, usually at high concentrations (mM range), increases extracellular level of dopamine, in in vivo microdialysis studies (3,41,62,69), although DHPG (3–300 μM) did not affect dopamine release in the nucleus accumbens (19). 1S,3R-ACPD-stimulated behavior was also correlated well with increases in striatal dopamine and dopamine metabolites (48). Recently, rotations induced by intracaudate DHPG or 1S,3R-ACPD was blocked by a dopamine D_1 receptor antagonist (15). Hyperlocomotion induced by injection of ACPD into the nucleus accumbens was also antagonized by the coinjection of a dopamine receptor antagonist (27) or by the dopamine depletion (36). These data support a dopaminergic dependency for mGluR-mediated behavioral stimulation. However, blockade of D_1 receptors in this study with systemic SCH-23390 at the dose that blocked behavioral responses to direct or indirect dopamine agonists (75,79) had no effect on DHPG-stimulated behaviors. This argues against the likelihood that dopamine is indirectly linked to behavioral changes induced by DHPG. Furthermore, the time course and the characteristic stereotypy that DHPG produced differ from that in response to dopamine stimulation. Thus, if at all there was increase in dopamine release in response to DHPG administration, such a release was dissociable from DHPG-stimulated behavior. Besides dopamine, 1S,3R-ACPD increased glutamate release in the dorsal striatum (28,50). However, a recent study in this laboratory found that the NMDA or kainate/AMPA receptor antagonist had no significant effect on DHPG-stimulated behavior (30). This argues against the participation of the ionotropic glutamate receptor activation in the DHPG effects.

Unlike the ionotropic receptors, mGluRs appear to exert dual effects on excitotoxicity in the CNS, depending upon the subgroups involved. Activation of the group I mGluRs with high doses of 1S,3R-ACPD (500–1000 nmol) or DHPG augments NMDA-induced, or directly causes NMDA and non-NMDA receptor-independent, neuronal death in neonatal (32,33) or adult (8,48,80,82) rats. In contrast, activation of the group II or III mGluRs with low dose of 1S,3R-ACPD (<100 nmol) or the subgroup-specific agonists is neuroprotective (7). In this study, DHPG was administered in doses ranging from 20–160 nmol. This seems to be safe dose range (subtoxic) because no evident of massive cell death was found in the tissue surrounding the injection tip. Moreover, the behavioral responses to DHPG was repeatable to the comparable extent 2 days after the initial experiment in the same rats tested. Feeley Kearney et al. (15) also reported a lack of the histological evidence of toxicity 24–48 h after acute intracaudate injection of DHPG at higher doses (500–1000 nmol).

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