

## Electrophysiological Characterization of AMPA and NMDA Receptors in Rat Dorsal Striatum

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The striatum receives glutamatergic afferents from the cortex and thalamus, and these synaptic transmissions are mediated by  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors. The purpose of this study was to characterize glutamate receptors by analyzing NMDA/AMPA ratio and rectification of AMPA and NMDA excitatory postsynaptic currents (EPSCs) using a whole-cell voltage-clamp method in the dorsal striatum. Receptor antagonists were used to isolate receptor or subunit specific EPSC, such as (DL)-2-amino-5-phosphonovaleric acid (APV), an NMDA receptor antagonist, ifenprodil, an NR2B antagonist, CNQX, an AMPA receptor antagonist and IEM-1460, a GluR2-lacking AMPA receptor blocker. AMPA and NMDA EPSCs were recorded at  $-70$  and  $+40$  mV, respectively. Rectification index was calculated by current ratio of EPSCs between  $+50$  and  $-50$  mV. NMDA/AMPA ratio was  $0.20 \pm 0.05$ , AMPA receptor ratio of GluR2-lacking/GluR2-containing subunit was  $0.26 \pm 0.05$  and NMDA receptor ratio of NR2B/NR2A subunit was  $0.32 \pm 0.03$ . The rectification index (control  $2.39 \pm 0.27$ ) was decreased in the presence of both APV and combination of APV and IEM-1460 ( $1.02 \pm 0.11$  and  $0.93 \pm 0.09$ , respectively). These results suggest that the major components of the striatal glutamate receptors are GluR2-containing AMPA receptors and NR2A-containing NMDA receptors. Our results may provide useful information for corticostriatal synaptic transmission and plasticity studies.

**Key Words:** Striatum, AMPA, Glutamate receptor, NMDA, Patch clamp

### INTRODUCTION

The striatum plays a key role in movement control and habitual formation. It receives glutamatergic afferents from the cortex and thalamus. These glutamatergic synaptic transmissions are mediated by  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors and *N*-methyl-D-aspartate (NMDA) receptors. The NMDA receptors are heteromeric assemblies of NR1 and NR2 subunits; the NR2 subunit is an essential factor in the biophysical and pharmacological properties of NMDA receptors, and can influence NMDA receptor assembly, ion conductance and synaptic plasticity (Bliss and Collingridge, 1993; Lau and Zukin, 2007). The NR2A subunit confers a lower affinity for both glutamate and NMDA, distinctly faster kinetics and higher channel open probability than does the NR2B subunit, which confers slower channel kinetics and reduced open probability (Parsons et al., 1998; Lau and Zukin, 2007). Earlier reports showed that long-term potentiation (LTP) is dependent on NR2A subunit, whereas NR2B subunit is involved in the induction of long-term depression (LTD) in

the hippocampus and cortex (Liu et al., 2004; Massey et al., 2004). Interestingly, another report suggested that NR2A subunit was not required for NMDA receptor dependent LTP in the whole brain region (Weitlauf et al., 2005). However, a different report suggested that activation of both NR2A and NR2B subunits was required for LTP in nucleus accumbens (Schotanus and Chergui, 2008). AMPA receptors consist of GluR1-4 subunits, and the presence or absence of GluR2 subunit characterizes physiological properties of AMPA receptors. For example, GluR2-containing AMPA receptors are  $\text{Ca}^{2+}$  impermeable and have linear rectification pattern, whereas GluR2-lacking AMPA receptors are  $\text{Ca}^{2+}$  permeable and have inward rectification pattern (Adesnik and Nicoll, 2007; Derkach et al., 2007).

The NMDA/AMPA ratio was reported using the electrophysiological method (McDermott et al., 2006; Kreitzer and Malenka, 2007; Du et al., 2008), and glutamatergic receptor subunit component ratio was shown through immunohistochemical studies in several brain regions (Nansen et al., 2000; Greger et al., 2002). However, the composition of the NMDA and AMPA receptor subunits has not been well established using electrophysiological methods in the dorsal striatum. Thus, the purpose of the present study was to

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**ABBREVIATIONS:** AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionate; NMDA, *N*-methyl-D-aspartate; EPSC, excitatory postsynaptic current; APV, (DL)-2-amino-5-phosphonovaleric acid; LTP, long-term potentiation; LTD, long-term depression.

characterize the AMPA and NMDA receptors including their subunit ratio, NMDA/AMPA ratio, and rectification pattern within the dorsal striatum using electrophysiological methods with specific receptor antagonists.

## METHODS

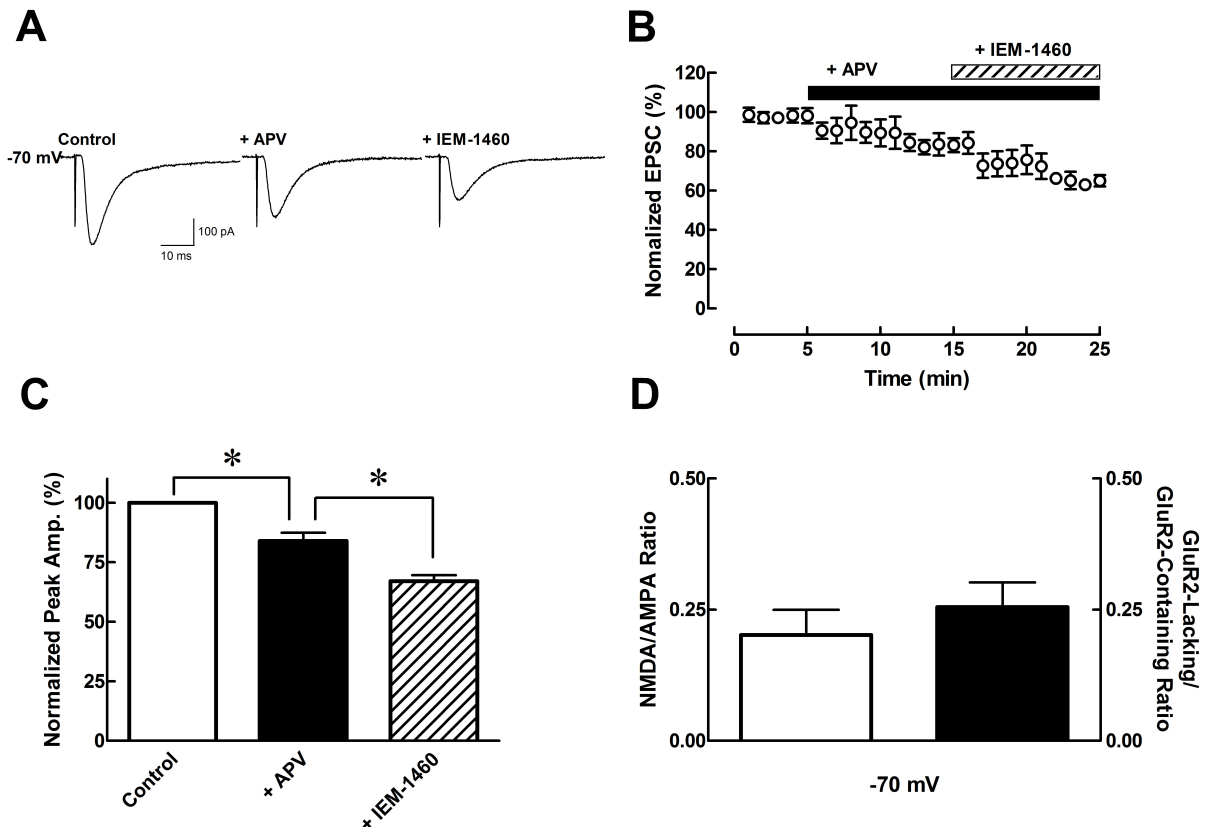
### Slice preparation

Brain slices were prepared from 15 to 21-day-old Sprague-Dawley rats using a previously described technique (Choi et al., 2006; Cho et al., 2008). A coronal slice (300  $\mu$ m thick) containing the cerebral cortex and striatum was produced using a manual vibratome (Campden Instruments, Loughborough, UK). The rats were anesthetized with pentobarbital (50 mg/kg, i.p.) and decapitated in conformity with the National Institutes of Health Guide for The Care and Use of Laboratory Animals. The brain slices were removed and placed in ice-cold, modified artificial cerebrospinal fluid (aCSF) containing (in mM) 194 sucrose, 30 NaCl, 4.5 KCl, 1 MgCl<sub>2</sub>, 26 NaHCO<sub>3</sub>, 1.2 NaH<sub>2</sub>PO<sub>4</sub> and 10 D-glucose adjusted to pH 7.4 by bubbling with 95% O<sub>2</sub>/5% CO<sub>2</sub>. The brain slices were then transferred to aCSF containing (in mM) 124 NaCl, 4.5 KCl, 2 CaCl<sub>2</sub>, 1 MgCl<sub>2</sub>, 26 NaHCO<sub>3</sub>, 1.2 NaH<sub>2</sub>CO<sub>3</sub> and 10 D-glucose adjusted to pH

7.4 by bubbling with 95% O<sub>2</sub>/5% CO<sub>2</sub>. The slices were allowed to recover for at least 1 h in aCSF at room temperature. A hemi-slice, containing the cortex and striatum, was submerged in a recording chamber and constantly superfused with aCSF bubbled with 95% O<sub>2</sub>/5% CO<sub>2</sub>. The flow rate was maintained at 2~3 ml/min using a peristaltic pump (Miniplus 2, Gilson, France). The temperature of the bath solution was maintained at 31±1°C.

### EPSC recording

Whole-cell voltage-clamp recordings were performed as described previously (Sung et al., 2001; Cho et al., 2008). Electrical stimuli (0.05 Hz) were delivered through a bipolar, Teflon<sup>®</sup>-coated tungsten electrode placed in the white matter dorsal to the striatum and in close proximity to the recording electrode. The stimulus intensity was set to yield excitatory postsynaptic current (EPSC) amplitudes from 100 pA to 300 pA. Tight-seal whole-cell recordings were obtained using pipettes made from borosilicate glass capillaries pulled on a P-97 micropipette puller (Sutter Instruments, Novato, CA). Pipette resistance ranged from 3 M $\Omega$  to 5 M $\Omega$ , filled with an internal solution containing (in mM) 120 CsMeSO<sub>3</sub>, 5 NaCl, 10 tetraethylammonium chloride, 10 HEPES, 5 lidocaine *N*-ethyl bromide (QX-314) (Br<sup>2+</sup> salt), 1.1 EGTA, 4 ATP (Mg<sup>2+</sup> salt), 0.3 GTP (Na<sup>+</sup> salt),



**Fig. 1.** Pharmacological isolation of AMPA receptors. (A) Sample traces of EPSCs with continuously added specific antagonist such as APV (NMDA receptor antagonist, 50  $\mu$ M), and IEM-1460 (GluR2-lacking AMPA receptor blocker, 100  $\mu$ M), respectively. (B) Plot graph shows baseline, addition of APV, and IEM-1460 by 10 min interval, tendency decreased EPSCs by APV and IEM-1460 (n=6). (C) Bar graph shows average peak data normalized to control (open bar) currents. \* $p$ <0.05, when compared to control versus APV and APV versus IEM-1460. (D) Bar graph shows NMDA/AMPA ratio and GluR2-lacking AMPA receptor/GluR2-containing AMPA receptor ratio calculated by data from Fig. 1C. Data are expressed as mean±S.E.M.

pH adjusted to 7.2 with CsOH, osmolarity adjusted to  $300 \pm 10$  mOsm with sucrose. Medium-sized neurons within two or three layers below the surface of the slice were identified using an Olympus BX50WI (Tokyo, Japan) differential interference contrast microscope. Neurons were voltage-clamped at  $-70$  mV applying APV, an NMDA receptor antagonist, IEM-1460, a GluR2-lacking AMPA receptor blocker for AMPA receptor characterization. NMDA receptors were characterized by voltage clamp method at  $+40$  mV holding potential with CNQX, an AMPA receptor antagonist. Also ifenprodil, an NMDA receptor subunit NR2B antagonist was used to further characterize the NR2A subunit specificity. All EPSCs were recorded from the dorsal striatum in the presence of  $50 \mu\text{M}$  picrotoxin, a GABA<sub>A</sub> receptor antagonist, to suppress GABA<sub>A</sub>-mediated currents. The rectification was measured at peak amplitude between  $-70$  mV and  $+50$  mV by  $20$  mV intervals. EPSCs were recorded with an Axopatch 1D patch-clamp amplifier (Molecular Device, Sunnyvale, CA), filtered at  $5$  kHz, digitized at  $10$  kHz using a Digidata 1322A (Molecular Device), and stored on a personal computer using pClamp 9.2 software (Molecular Device). The series resistance was  $<25 \text{ M}\Omega$  and was not compensated. Both series and input resistance were monitored throughout the experiment by delivering  $5$  mV voltage steps. If the series resistance changed more

than 20% during the course of an experiment, the data was discarded.

### Data analysis

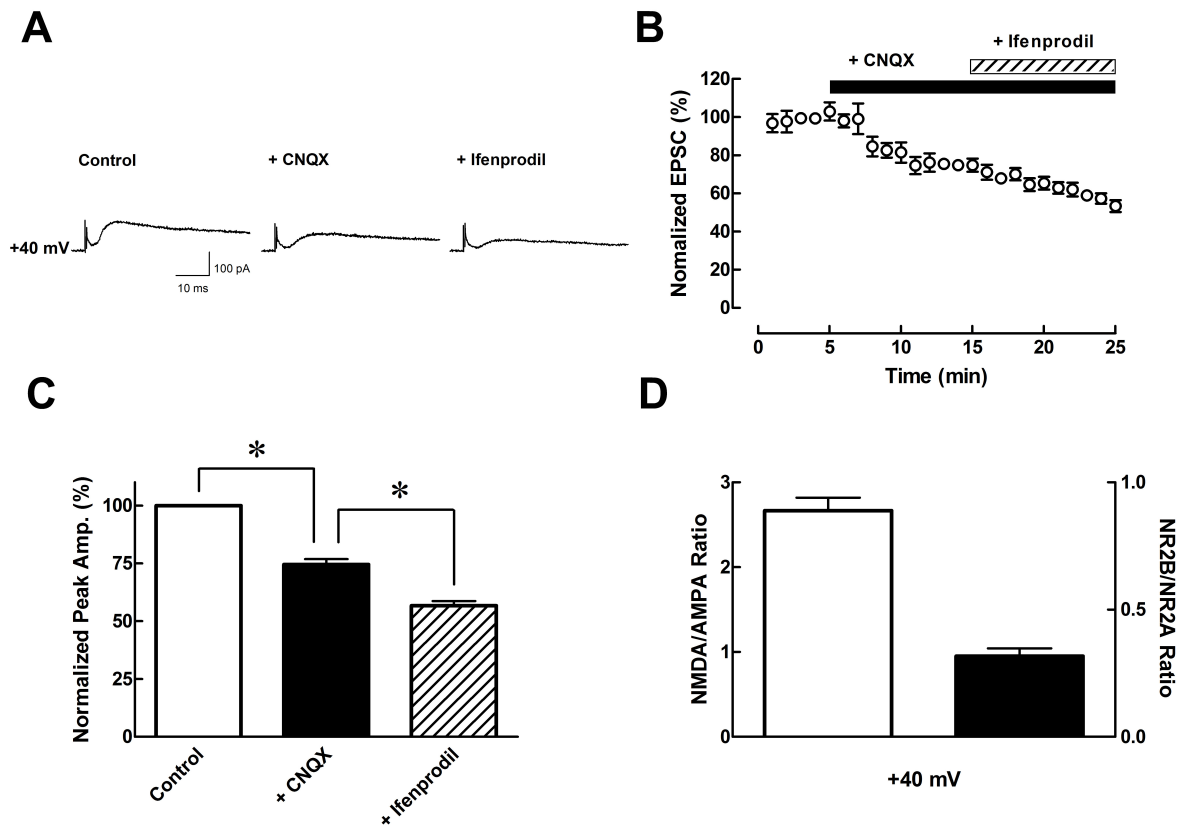
AMPA and NMDA-mediated EPSCs were analyzed by Clampfit 10.2 software (Molecular Device). All averaged data were presented as means  $\pm$  S.E.M.. Statistical significance was determined by the Student's *t*-test using Prism 4.0 software (Graph Pad Software, Avenida, CA).

### Drugs and chemicals

(DL)-2-amino-5-phosphonovaleric acid (APV), IEM-1460 and CNQX were purchased from Tocris Cookson (Avonmouth, UK). All other chemicals used in this study were purchased from Sigma-Aldrich (St. Louis, MO). Drugs were diluted with aCSF immediately before use from stock solutions prepared according to the manufacturer's instructions.

## RESULTS

To calculate the ratio of AMPA receptor, NMDA receptor and their subunits on striatal glutamatergic synapses, we



**Fig. 2.** Pharmacological isolation of NMDA receptors. (A) Sample traces of EPSCs with continuously added specific antagonist such as CNQX (AMPA receptor antagonist,  $10 \mu\text{M}$ ), and ifenprodil (NMDA receptor subunit NR2B blocker,  $3 \mu\text{M}$ ), respectively. (B) Plot graph shows baseline, addition of CNQX, and ifenprodil by 10 min interval, tendency decreased EPSCs by CNQX, and ifenprodil ( $n=6$ ). (C) Bar graph shows average peak data normalized to control (open bar) currents.  $*p < 0.05$ , when compared to control versus CNQX and CNQX versus ifenprodil. (D) Bar graph shows NMDA/AMPA ratio and NR2B/NR2A ratio calculated by data from Fig. 2C. Data are expressed as mean  $\pm$  S.E.M..

first isolated AMPA receptor-mediated currents at  $-70$  mV (Fig. 1). In the presence of APV ( $50 \mu\text{M}$ ), the normalized EPSCs were decreased by  $16.12 \pm 3.49\%$  ( $n=6$ ,  $p < 0.05$ ) of the control and in the presence of IEM-1460 ( $100 \mu\text{M}$ ), the EPSCs were decreased by  $32.96 \pm 2.53\%$  ( $n=6$ ,  $p < 0.05$ ) of the control (Fig. 1). The NMDA/AMPA ratio was calculated by the subtraction of EPSCs in the presence of APV from normal condition, and the GluR2-lacking/GluR2-containing ratio was calculated by the subtraction of EPSCs in the presence of APV and IEM-1460 from APV-treated only. The NMDA/AMPA ratio and the GluR2-lacking/GluR2-containing ratio was  $0.20 \pm 0.05$  and  $0.26 \pm 0.05$  at  $-70$  mV, respectively. The NMDA/AMPA ratio and subunit ratio were calculated from Fig. 1C (Fig. 1D).

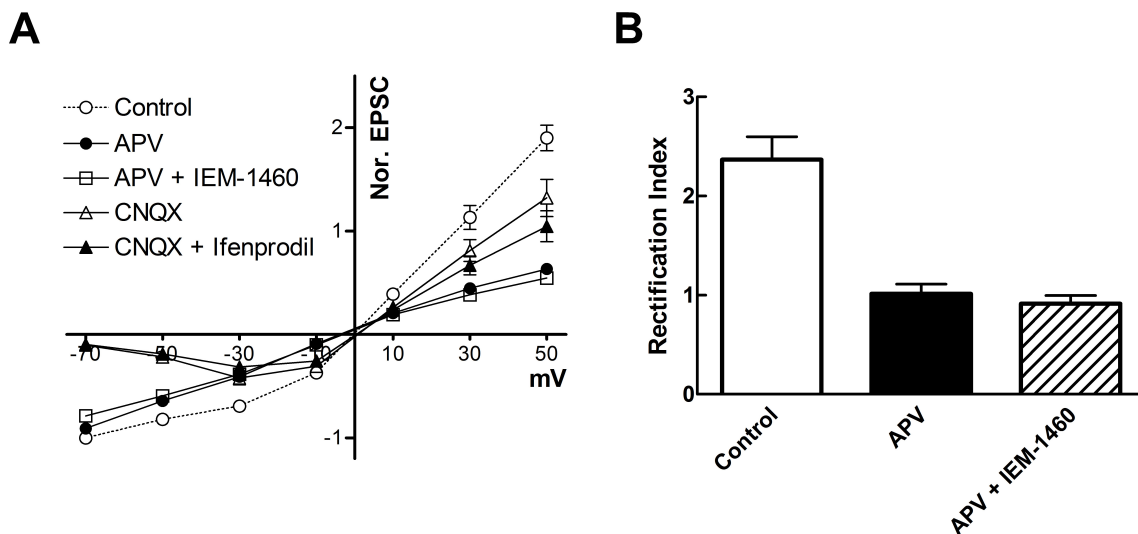
We then isolated NMDA receptor-mediated currents at  $+40$  mV (Fig. 2). EPSCs in the presence of CNQX ( $10 \mu\text{M}$ ) were decreased by  $25.48 \pm 2.36\%$  ( $n=6$ ,  $p < 0.05$ ) of control, and in the presence of ifenprodil ( $3 \mu\text{M}$ ), the EPSCs were decreased by  $43.31 \pm 2.05\%$  ( $n=6$ ,  $p < 0.05$ ) of the control (Fig. 2). The NMDA/AMPA ratio was calculated by subtraction of EPSCs in the presence of CNQX from absence of CNQX. The NR2B/NR2A ratio was calculated by the subtraction of EPSCs in the presence of CNQX and ifenprodil from CNQX-treated only. The NMDA/AMPA and NR2B/NR2A ratios were  $2.67 \pm 0.15$  and  $0.32 \pm 0.03$  at  $+40$  mV, respectively. Both these ratios were calculated from Fig. 2C (Fig. 2D).

The rectification pattern of AMPA receptor containing GluR2 subunit and NMDA receptor containing NR2A subunit was calculated using voltage clamp method (holding level was between  $-70$  mV and  $+50$  mV,  $20$  mV interval; Fig. 3A). The rectification index was calculated by the current/voltage relationship as the ratio of EPSCs amplitudes between  $-50$  and  $+50$  mV. The rectification pattern of AMPA receptors was linear by APV-treated currents. Also, the GluR2-containing rectification pattern was similar to APV-treated currents (current ratio between  $+50$  mV and  $-50$  mV; control,  $2.39 \pm 0.27$ ; APV,  $1.02 \pm 0.11$ ; combination of APV and IEM-1460,  $0.93 \pm 0.09$ ;  $n=7$ , Fig. 3B). Generally,

it is well known that GluR2 has a linear rectification pattern, and this was confirmed by our results showing that the GluR2-containing AMPA receptor exhibited a linear rectification pattern. To indicate the rectification pattern of the NMDA receptor, we studied the current/voltage relationship of NMDA receptors (Fig. 3A). The rectification pattern of CNQX-treatment was not significantly different from that of CNQX and ifenprodil-treatment (current ratio between  $+50$  mV and  $-50$  mV: control,  $2.32 \pm 0.24$ , CNQX,  $5.92 \pm 0.31$ ; combination of CNQX and ifenprodil,  $5.46 \pm 0.46$ ;  $n=7$ ). These results suggest that the major components of AMPA and NMDA receptors in the dorsal striatum were GluR2-containing AMPA receptors and NR2A-containing NMDA receptors.

## DISCUSSION

We isolated the glutamate receptor and subunit on striatal neurons. Our results showed that the predominant composition of AMPA receptors were GluR2-containing AMPA receptors at  $-70$  mV (Fig. 1). Also other immunological studies reported that GluR2 expression was higher than other subunits (Nansen et al., 2000; Greger et al., 2002). Furthermore, a study using IEM-1460 reported that the GluR2-containing AMPA receptor was the major component of the hippocampus (Buldakova et al., 2007). We isolated NMDA receptors and subunit currents at  $+40$  mV (Fig. 2). Our data showed that NR2A mediated currents were higher than NR2B at  $+40$  mV, when NMDA receptor activation was higher. An autoradiography study reported that the predominant NMDA receptor subunits were NR2A and NR2B in the striatum (Standaert et al., 1994). Recently other studies also reported that NR2A was expressed at higher levels than NR2B using electrophysiological and immunohistochemical methods in the striatum (Wang et al., 1995; Ding et al., 2008). Our results indicate that NR2A might be the functional property of the major NMDA re-



**Fig. 3.** Rectification pattern of synaptic responses in rat striatum. Current/voltage curve and bar graph shows the rectification pattern and the rectification index. (A) Current/voltage curve showing the rectification pattern of control, APV, combination of IEM-1460 and APV, CNQX and combination of ifenprodil and CNQX. (B) Bar graph showing the rectification index (current ratio between  $+50$  mV and  $-50$  mV) of control, APV and combination of APV and IEM-1460 ( $n=7$ ). Data are expressed as mean  $\pm$  S.E.M.

ceptor composition.

To investigate the rectification pattern of AMPA and NMDA receptors and their subunits, we first isolated the AMPA receptor and GluR2-containing AMPA receptor. Generally, the GluR2-containing AMPA receptor has a linear rectification pattern in comparison to the GluR2-lacking AMPA receptor on the hippocampal neuron (Adesnik and Nicoll, 2007; Derkach et al., 2007). Our results show that the GluR2-containing AMPA receptor has a linear pattern on striatal neurons (Fig. 3). Furthermore our data shows that the APV-treated pattern was linear. These data suggest that GluR2-containing AMPA receptor is the major component of the striatal AMPA receptor. The rectification pattern of NMDA receptors in the presence or absence of ifenprodil was not significantly different because the currents were very small at negative holding level. These findings suggest that the major component of NMDA receptors in the dorsal striatum are NR2A-containing NMDA receptors.

Generally, GluR2-containing AMPA receptors show properties of  $\text{Ca}^{2+}$  impermeability, low channel conductance and a linear rectification pattern, whereas GluR2-lacking AMPA receptors exhibit  $\text{Ca}^{2+}$  permeability, high channel conductance and an inward rectification pattern (Jonas and Burnashev, 1995; Adesnik and Nicoll, 2007; Derkach et al., 2007; Panicker et al., 2008). Moreover, the presence or absence of the GluR2 subunit can alter AMPA receptor properties and synaptic transmission (Derkach et al., 2007). These subunits relate to receptor trafficking (Tardin et al., 2003) and determine synaptic plasticity (Adesnik and Nicoll, 2007; Derkach et al., 2007). Another report suggested that GluR2-lacking AMPA receptors do not play a key role in LTP in the most commonly used preparation for studying hippocampal synaptic plasticity (Adesnik and Nicoll, 2007). Our results show that the predominant AMPA receptor component was the GluR2-containing AMPA receptor in the striatum at near resting membrane potential. Although it has not yet been proven, these results suggest the possibility that the GluR2-containing AMPA receptor may contribute to modulation of the striatal synaptic plasticity such as LTP and LTD, though its high  $\text{Ca}^{2+}$  permeability and involvement in AMPA receptor trafficking.

Meanwhile, NR2A of the NMDA receptor subunit confers a lower affinity for glutamate and NMDA, distinctly faster kinetics and higher channel open probability than NR2B. It has also been established that the NMDA receptor subunits play a key role in synaptic plasticity (Parsons et al., 1998; Massey et al., 2004; Weitlauf et al., 2005; Lau and Zukin, 2007). Another report suggested that the NR2A subunit was not required for NMDA receptor dependent LTP in the whole brain region (Weitlauf et al., 2005). However, NR2A-containing NMDA receptors have more prominent  $\text{Ca}^{2+}$ -dependent desensitization and slower receptor trafficking than NR2B-containing NMDA receptors (Lau and Zukin, 2007), and also our results showed that NR2A-containing NMDA receptors are the major component of the striatum. These results suggested that NR2A-containing NMDA receptors might have an important role in modulating striatal synaptic plasticity though its higher  $\text{Ca}^{2+}$  conductance, and lower receptor trafficking compared to NR2B-containing NMDA receptors. However, further studies are necessary to verify whether the distinctive differences in striatal NMDA and AMPA receptor subunit composition relate to synaptic plasticity, because it is unclear that which AMPA and NMDA receptor subunits relate to synaptic

plasticity in the striatum. In conclusion, our results suggest that GluR2-containing AMPA receptors and NR2A-containing NMDA receptors are principal glutamatergic receptors in the dorsal striatum, and these subunits specificity might contribute to the characteristic pattern of synaptic transmission and plasticity in this brain region.

## ACKNOWLEDGEMENT

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