EXPRESSION OF N-METHYL-D-ASPARTATE RECEPTOR-DEPENDENT LONG-TERM POTENTIATION IN THE NEOSTRIATAL NEURONS IN AN IN VITRO SLICE AFTER ETHANOL WITHDRAWAL OF THE RAT

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Abstract—To examine changes in corticostriatal synaptic transmission in rats with ethanol withdrawal syndrome, intracellular and extracellular responses to subcortical white matter stimulation were recorded in neostriatal slice preparations. The resting membrane potential, input resistance and depolarizing postsynaptic potentials to single cortical white matter stimulation were similar in the neostriatum of naive and ethanol withdrawal rats. Repetitive stimulation of the white matter induced more pronounced N-methyl-d-aspartate receptor-mediated postsynaptic potentials in ethanol withdrawal than naive rat neostriatum. In intracellular recording, tetanic stimulation (50 Hz, 20 s) induced more pronounced post-tetanic potentiation of depolarizing postsynaptic potentials in the neostriatum of ethanol withdrawal than naive rats. However, in extracellular recording, tetanic stimulation induced smaller post-tetanic depression of population spikes in the neostriatum of ethanol withdrawal than naive rats. Tetanic stimulation of the subcortical white matter induced long-term potentiation of postsynaptic potentials and population spikes in the ethanol withdrawal rat neostriatum, while long-term depression was evoked in the naive rat neostriatum. The induction of long-term potentiation was blocked by d-2-amino-5-phosphonovaleric acid or 7-chlorokynurenic acid, N-methyl-d-aspartate receptor antagonists, but not by (RS)-methyl-4-carboxyphenyl-glycine, a metabotropic glutamate receptor antagonist. Dopamine also significantly depressed the induction of long-term potentiation in ethanol withdrawal rat neostriatum and this depressant effect was antagonized by the D₂ antagonist L-sulpiride but not by the D₁ antagonist SCH23390.

These results indicate that the N-methyl-d-aspartate component of the corticostriatal glutamatergic responses, which might be necessary for induction of long-term potentiation, was enhanced in ethanol withdrawal rats. The depression of long-term potentiation induction by activation of D₂ receptor suggests that corticostriatal N-methyl-d-aspartate response or intracellular mechanisms involving in the induction of the long-term potentiation can be suppressed by D₂ activation and that the D₂ effects are inhibited in the neostriatum of ethanol withdrawal rats. © 1999 IBRO. Published by Elsevier Science Ltd.

Key words: ethanol withdrawal, long-term potentiation, long-term depression, NMDA receptor, dopamine, dopamine D₂ receptor.

It is well documented that a cessation of long-term intake of ethanol results in an ethanol withdrawal (EW) syndrome characterized by convulsion, tremor and other signs of hyperexcitability of the CNS. Despite its clinical importance, the understanding of the physiological basis of the withdrawal syndrome is limited. There is increasing evidence that the N-methyl-d-aspartate (NMDA) receptor is involved in the development of EW syndrome. EW increases number of NMDA receptors, facilitates NMDA receptor-mediated synaptic responses and NMDA excitotoxicity in the hippocampus. Furthermore, EW seizures are effectively suppressed by systemic application of the NMDA antagonist dizocilpine maleate (MK-801). The involvement of dopamine (DA) receptors has also been postulated in the development of EW syndrome since [3H]DA release from neostriatal slice preparations evoked by high K⁺ is decreased following EW.

Turnover rates of DA following EW are also reported to be decreased in various
brain regions including the neostriatum. The mesolimbic DAergic neuronal activity is markedly reduced following EW.15 L-DOPA and intracranially injected DA lowered EW seizures while haloperidol increased seizures.1 The prime candidate for the brain site where both NMDA and DA receptors can exert behavioral effects is the neostriatum.

The neostriatum receives massive cortical inputs which are mediated by both α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors and NMDA receptors.11,21,23,24 The NMDA receptor-mediated response is small when the cortical inputs evoked small subthreshold excitatory postsynaptic potentials (EPSPs) while the NMDA response contributes significantly to evoke spikes when the cortical inputs are strong enough to depolarize the neurons near to the threshold level.11,23,24 The neostriatum also receives massive mesostriatal DAergic afferent projections. DA exerts various physiological effects on neostriatal neurons.2,8 The direct effect of DA on the firing activity of the neostriatal spiny neurons is generally inhibitory, although a number of mechanisms might be involved in the inhibition.2,8 DA also alters the activity of neostriatal neurons by modulating the cortical inputs. Two mechanisms for the DA modulation of the cortical inputs are reported. First, DA affects the presynaptic glutamate release mechanism and depresses the excitatory synaptic transmission.18,22,27 Second, DA depresses the excitatory synaptic transmission in the neostriatum through postsynaptic DA receptors.6,38

High-frequency activation of the corticostriatal inputs results in long-term depression (LTD) or long-term potentiation (LTP).2,8 These plasticities at glutamatergic synapses on the neostriatal neurons are postulated to be involved in the movement control and cognitive function of the neostriatum. The conditions that induce LTD and LTP, and the mechanisms that underlie the induction of LTD and LTP are still unclear. In slice preparations, high-frequency stimulation of the cortical inputs induces LTD. Calabresi et al. have shown that co-activation of D1 and D2 receptors is required for LTD in the neostriatum.3,4 The induction of LTP in the neostriatum slices is reported to occur when the voltage-dependent NMDA channels were removed7–9 or when DA was applied locally to the recording neuron during high-frequency stimulation.41 In anesthetized rats, high-frequency cortical stimulation of the motor cortex in combination with intracellular depolarization of postsynaptic neostriatal neurons induced LTP in the recording neurons.10 The induction of LTD is not affected by blockade of GABAA, AMPA or NMDA receptors.4,26,40 Activation of metabotropic receptors reduces glutamatergic and GABAergic postsynaptic potentials in the neostriatum.5,12,25,37 Metabotropic receptors have been found to play a role in LTD in the neostriatum,4,8 while its involvement in LTP has not been reported.

The present study aimed to investigate possible changes in plasticity at cortical glutamatergic synapses on neostriatal neurons in in vitro slice preparations from EW rats.

**EXPERIMENTAL PROCEDURES**

**Animals and treatments**

Male Wistar rats (four weeks old; Seac Yoshimitsu, Fukuoka, Japan) were individually housed and chronically administered ethanol by feeding with a liquid diet (Oriental Yeast Co., Tokyo, Japan) containing ethanol through vertical watering tubes according to the method described previously.30,31 Shortly, after two days of liquid diet administration, animals were fed on liquid diets containing increasing concentrations of ethanol. To avoid the natural aversion of rats to alcohol, the percentage of ethanol was started at 2% (v/v) and was increased by 1% every two days up to 5%. The daily consumption of 2–4% ethanol diets was 60 to 80 ml. The ethanol-treated rats were fed on 5% ethanol diet for a further 10 days with daily consumption of 40–50 ml. The rats received ethanol for 16 days were visibly intoxicated since their locomotor activity was markedly decreased. At the end of this period, all rats were withdrawn from ethanol at 15–20 h before the slice experiment. Control rats maintained under similar conditions were fed on a standard liquid diet for the same period. All rats withdrawn from ethanol for 15–20 h exhibited clear behavioral symptoms of hypereexcitability including increased startle responses and spontaneous seizures. Two out of 31 EW rats had tonic seizures followed by respiratory arrest and died. Naive and the remaining 29 EW rats were tested for withdrawal signs. Withdrawal symptoms were quantified by following behavioral scores used by Davidson et al.45: 0 = no change; 1 = hunched body, isolated wet dog shakes, piloerection, rotation on the spot, jaw chattering or slow rotation around cage; 2 = general hyperactivity, rapid rotation around cage, series of wet dog shakes, vocalization or moderate escape reaction; 3 = barrel rolls, wild running, rearing and falling or moderate escape reaction; 4 = tonic–clonic seizure or strong escape reaction. Rats were observed for 30 min and received a score if any one of these behaviors was detected. The mean behavioral score of EW rats (9.6 ± 0.1, n = 29) was significantly higher than that of the naive rats (1.3 ± 0.2, n = 10, P < 0.001, Student’s t-test). The number of EW and naive rats used for electrophysiological analyses was 29 and 10, respectively.

**Preparation of neostriatal slices**

Normal and EW rats were decapitated under light ether anesthesia. The brains were rapidly removed, parasagittal slices (400 μm thick) were cut on a Vibroslice (Vibroslice 752M, Campden Instruments) and the slices were trimmed to include the neostriatum and the cortex in ice-cold Krebs–Ringer solution.

**Electrophysiology**

Detailed recording methods have been described elsewhere.30,31 In brief, a single slice was placed in an interface-type recording chamber at a constant bath temperature of 36 ± 0.1°C. Intracellular recordings from striatal neurons were obtained through glass microelectrodes filled with 2 M K-citrate and had a high impedance amplifier (Nerodata IR 183). Electrical stimulation (intensity 1–20 V, duration 200 μs, frequency 0.6 Hz) was applied to the subcortical white matter through a bipolar
electrode. Tetanic stimuli were delivered at 50 Hz for 20 s. Electrical responses were stored in a videocassette recorder through a PCM converting processor (VR-10B, Instrutech Corporation) and plotted on an X–Y plotter. Extracellular field potentials were recorded with glass microelectrodes filled with the Krebs solution and placed on the surface of the slice preparation. The average of four consecutive responses was displayed on a digital storage oscilloscope and plotted on an X–Y plotter. The population spike amplitude was measured from the peak negativity to the line joining the pre- and post-spike population EPSPs. The Krebs solution for superfusion of the slices was composed of (in mM): NaCl 124.0, KCl 5.0, KH2 PO 4 1.24, NaHCO 3 26.0, CaCl 2 2.4, MgSO 4 1.3 and glucose 10.0. The following drugs were used for bath application: 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, Research Biochemicals), d-2-amino-5-phosphonovaleric acid (APV, Sigma), 7-chlorokynurenic acid (7-Cl-KYN, Research Biochemicals), (RS)-methyl-4-carboxyphenyl-glycine (MCPG, Tocris Cookman), dopamine (DA, Sigma), nomifensine (RBI), L-ascorbic acid (Hayashi), R(+) -SCH23390 (Research Biochemicals), L-sulpiride (Sigma). DA was dissolved in perfusing Ringer solution with ascorbic acid (300 μM, Hayashi) and nomifensine malate (1 μM, RBI). Numerical data are represented as mean ± S.E.M. The number of neurons and slices is shown in parentheses for intracellular and extracellular data, respectively.

RESULTS

Membrane properties of neostriatal neurons

The passive membrane properties such as the resting membrane potential and the input resistance of neostriatal neurons from naive and EW rats were not significantly different (Table 1). There was also no significant difference between the mean latency and amplitude of depolarizing postsynaptic potentials (DPSPs) evoked by single subspike stimulation of the subcortical white matter in neostriatal neurons from naive and EW rats (Table 1). The DPSPs evoked in neostriatal neurons from naive and EW rats were almost completely suppressed by CNQX (4 μM) (data not shown). These observations indicate that the conduction time of the corticostriatal fibers and the threshold of the neostriatal neurons were similar in naive and EW rats.

When repetitive subspike electrical stimulation (eight stimuli with 5 ms interspike intervals) were applied to the subcortical white matter, the postsynaptic responses of striatal neuron were clearly different between the naive and EW rats. In the slice obtained from naive rats, repetitive stimulation induced DPSPs with a slow falling phase in striatal neurons (Fig. 1A). In contrast, in slices obtained from EW rats, DPSPs were followed by plateau-like potentials. APV (50 μM) strongly suppressed the plateau-like potential.

Table 1. Passive membrane properties and depolarizing postsynaptic potentials of neostriatal neurons in naive and ethanol withdrawal rats

<table>
<thead>
<tr>
<th></th>
<th>Naive</th>
<th>EW</th>
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<tbody>
<tr>
<td>Resting membrane potential, mV</td>
<td>−75.4 ± 0.8 (5)</td>
<td>−74.1 ± 1.7 (7)</td>
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<tr>
<td>Input resistance, MΩ</td>
<td>24.4 ± 1.6 (5)</td>
<td>23.2 ± 1.7 (6)</td>
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<tr>
<td>DPSPs latency, ms</td>
<td>2.3 ± 0.2 (6)</td>
<td>2.7 ± 0.1 (6)</td>
</tr>
<tr>
<td>DPSPs amplitude, mV</td>
<td>15.4 ± 1.4 (5)</td>
<td>15.6 ± 0.8 (6)</td>
</tr>
<tr>
<td>Half duration of DPSPs evoked by repetitive stimulation, ms</td>
<td>28.2 ± 4.0 (6)</td>
<td>50.7 ± 8.4 (6)*</td>
</tr>
</tbody>
</table>

Values represent mean ± S.E.M. *P < 0.05 as compared with Naive (Student’s t-test). The number of neurons is shown in parentheses.
Expression of long-term potentiation in neostriatal neurons of ethanol withdrawal rats

In all neostriatal neurons recorded in the slices from naive rats, tetanic stimulation (50 Hz, 20 s) of the subcortical white matter induced post-tetanic potentiation (PTP) of DPSPs that lasted for 1–5 min, and then the amplitude of DPSPs was decreased (Fig. 2A). The decrease of the DPSP amplitude lasted for more than 20 min and thus was considered to be LTD. The relative amplitude of the DPSPs measured at 20 min after tetanic stimulation was 92.9 ± 14.3% (n = 5). By contrast, in the neostriatal slices of EW rats, tetanic stimulation elicited much pronounced PTP, and the PTP was followed by LTP of the DPSPs that lasted for at least 20 min. The increased PTP and LTP were observed in five out of six neostriatal neurons recorded from EW rats (Fig. 2B). One of the six neurons tested did not show observable changes in the amplitude of the DPSPs. The relative amplitude of the DPSPs measured at 20 min after tetanic stimulation was 120.5 ± 2.7% (n = 6). Because of the pronounced PTP and LTP, the mean relative amplitude of DPSPs recorded in neostriatal neurons after the tetanic stimulation from EW rats was significantly larger than that from the naive rats (Fig. 2C). The LTP of the DPSPs was not associated with alterations in the resting membrane potential or the input resistance of the neurons.

Because previous studies indicated that tetanic stimulation of the cortex induced LTD of the population spike in the neostriatum,4,26,39 we also performed similar tests in the neostriatum of EW rats. In neostriatal slices from the naive rats, the amplitude of population spikes was significantly reduced after the tetanic stimulation (Fig. 3, Table 2), a result consistent with previous observations on neostriatal LTD.4,26,39 In the neostriatum of EW rats, the tetanic stimulation induced a different pattern of change in the population spike amplitude. The population spike amplitude was transiently depressed and
then gradually increased after tetanic stimulation. At approximately 30 min after tetanus, the population spike amplitude reached a stable level of enhancement forming LTP (Fig. 3). The relative amplitude of population spikes after tetanic stimulation was significantly larger than that from naive rats (Fig. 3B, Table 2).

In intracellular recording, tetanic stimulation
induced transient PTP of DPSPs amplitude in neostriatal neurons whereas, in field potential recording, the same tetanic stimulation induced transient depression of the population spike amplitude. Thus, the short-term depression of the population spike is not due to a decrease in transmitter release which occurs after high-frequency burst stimulation.\textsuperscript{26} Intracellular current pulse stimulation experiments indicated that the spike threshold of neostriatal neurons was transiently elevated following tetanic stimulation (data not shown).

**Effects of glutamate receptor antagonists on long-term potentiation of ethanol withdrawal rats**

The involvement of glutamate receptors in the development of LTP in the other brain areas has been well demonstrated.\textsuperscript{32} Previous studies on neostriatal LTD of naive rats have also dealt with the effects of glutamate antagonists.\textsuperscript{4,26,39} Therefore, we examined the effects of glutamate receptor antagonists on the induction of LTP in neostriatal slices from EW rats. Antagonists were applied to the perfusing Krebs solution 30 min before tetanic stimulation. When tetanic stimulation was applied during application of APV (50 \u00b5M), the induction of LTP of population spike in the neostriatal slices was completely suppressed (Fig. 4, Table 2). When 7-Cl-KYN (30 \u00b5M), a glycine site antagonist of NMDA receptor, was present during tetanic stimulation, the induction of LTP was also completely suppressed (Fig. 4, Table 2). Returning to the control Ringer solution immediately after tetanic stimulation did not save LTP of the population spike amplitude. The induction of the transient depression of the population spikes was not affected by either APV or 7-Cl-KYN. To assess the possibility that metabotropic glutamate receptor are involved in the induction of LTP, effects of MCPG, a metabotropic glutamate receptor antagonist, were examined. Bath application of MCPG suppressed the transient depression after tetanic stimulation and unmasked pronounced PTP of population spike, while the induction of LTP was not affected (Fig. 4, Table 2).

The results of the experiments with NMDA antagonists described above suggest that the induction of LTP in the EW rats may be due to an increase in NMDA receptor-mediated responses. To test this possibility, we examined the effects of tetanic cortical stimulation in the slices obtained from naive rats under the Mg\textsuperscript{2+}-free condition which is known to fully activate the NMDA receptor-mediated component of synaptic responses. The tetanic cortical stimulation induced pronounced PTP and the enhancement of the population spike amplitude lasting up to 20 min after tetanic stimulation. The amplitude of population spikes, however, was returned to the pre-tetanus level within 30 min after tetanic stimulation (Fig. 4C, Table 2), indicating that this observation was a short-term potentiation rather than LTP and that an enhancement of NMDA response alone is not enough to induce LTP. In the neostriatal slices from EW rats, tetanic cortical stimulation-induced pronounced PTP was followed by LTP of population spikes (Fig. 4C). The relative population spike amplitude measured at 30 min after tetanus was similar to that obtained in the control, Mg\textsuperscript{2+} containing, Krebs solution (Table 2). These observations indicate that the activation of NMDA receptors further potentiate the magnitude of LTP of population spike in neostriatal slices of EW rats, while it is insufficient to induce LTP in the neostriatal slices obtained from naive rats.

**Effects of dopamine on long-term potentiation in the neostriatum of ethanol withdrawal rats**

We next examined effects of DA on the induction of LTP in the neostriatum of EW rats, since the induction of LTD in the neostriatal slices obtained from naive rats is dependent on the activation of DA receptors\textsuperscript{3,4,9} and we have recently shown that tetanic stimulation with a relatively low frequency (20 Hz, 5 s) produces a long-term enhancement of DA release in the neostriatal slices.\textsuperscript{33} DA was applied to the perfusing Krebs solution with a final concentration of 30 \u00b5M dissolved in ascorbic acid (300 \u00b5M) and nomifensine (1 \u00b5M) 30 min before tetanic stimulation. Bath application of DA slightly, about 10%, but not significantly depressed the amplitude of population spikes. When tetanic stimulation was applied during application of DA, the induction of LTP in the neostriatal slices from EW rats was significantly suppressed (Fig. 5, Table 2). At the same time, the degree of the transient depression evoked by tetanic stimulation was significantly increased during application of DA (P < 0.05, Student’s t-test). In order to determine the receptor types involved in the depressant effect of DA on the induction of LTP, \(R^\parallel\)-SCH23390, a D\textsubscript{1} receptor antagonist, or L-sulpiride, a D\textsubscript{2} receptor antagonist, was applied with DA. \(R^\parallel\)-SCH23390 (1 \u00b5M) had no significant effect on the depressant effect of DA on the induction of LTP (Fig. 5, Table 2). The depressant effect of DA was significantly antagonized by L-sulpiride (1 \u00b5M) (Fig. 5, Table 2).

**DISCUSSION**

The major finding of the present study was that relatively low-frequency (50 Hz, 20 s) tetanic stimulation induced NMDA-receptor dependent LTP in the neostriatum of EW rats. Electrophysiological studies suggest that corticostral inputs are mediated by both AMPA/kainate and NMDA receptors. The NMDA-receptor mediated responses became a significant component when neostriatal neurons were sufficiently depolarized by current injection\textsuperscript{11} or by strong repetitive cortical stimulation.\textsuperscript{24} Repetitive or tetanic stimulation could
enhance NMDA responses by multiple mechanisms. An increase in the extracellular K$^+$ would result in membrane depolarization and contribute to enhance NMDA receptor-mediated response by removing the voltage-dependent Mg block of NMDA channels. The accumulation of extracellular K$^+$ may also depress the efficacy of GABA_A receptor-mediated inhibition and contribute further to depolarize neurons.

Recently, Morrisett reported that NMDA receptor-dependent afterdischarges in rat dentate gyrus were potentiated after \textit{in vitro} EW. This observation was consistent with the observation that the hippocampus of the EW rat has reduced GABA_A

Fig. 4. Effects of glutamate antagonists and removal of Mg$^{2+}$ on the induction of LTP in population spikes evoked in neostriatal slices from EW and naive rats. (A) Superimposed records of population spikes (average of four successive responses) evoked in neostriatal slices obtained from EW rats before (1) and 30 min after (2) tetanic stimulation (50 Hz, 20 s) during application of glutamate antagonists, APV (50 µM), 7-CI-KYN (30 µM) and MCPG (250 µM). (B) Time-course of changes in the amplitude of population spikes evoked in neostriatal slices obtained from the EW rats after tetanic stimulation during application of APV (50 µM, $n = 5$), 7-CI-KYN (30 µM, $n = 4$) and MCPG (250 µM, $n = 4$). (C) Effects of tetanic cortical stimulation on population spike amplitude under the Mg$^{2+}$-free condition in the neostriatal slices of naive ($n = 9$) and EW rats ($n = 5$). Asterisks indicate significant differences between naive and EW rats (*$P < 0.05$, **$P < 0.01$; Student’s \(t\)-test).
receptor functions and an increased number of NMDA receptors. Whether similar changes occur in the neostriatum of EW rats has not been tested. We tested the possibility that an increase in the NMDA response alone could induce LTP. Superfusion of Mg²⁺-free medium resulted in strong PTP without following LTP in the naive rat neostriatum. This observation was very similar to the observations made by Walsh and Dunia, in which they showed that there was a tendency towards the expression of short-term potentiation but not LTP following tetanic stimulation in the neostriatal neurons under Mg²⁺-free conditions. Taken together, we speculate that the NMDA receptor-mediated component of synaptic responses was enhanced in the neostriatum of EW rats, whereas the enhancement was not sufficient for induction of LTP following tetanic cortical stimulation.

The induction of LTP in the neostriatum of EW rats after tetanic cortical stimulation was significantly suppressed by D₂ receptor activation. It has been reported that DAergic transmission in the neostriatum of EW rats is impaired. [³H]DA release evoked by high-K⁺ in the neostriatal slice preparations is decreased. Turnover rates of DA are also decreased following EW in various brain regions including the neostriatum. Thus it can be speculated that an impairment in DAergic transmission plays a pivotal role in the expression of LTP. Recently, Calabresi et al. have reported that trains of tetanic cortical stimulation (100 Hz for 1–3 s) at a 10–20 s interval induced an NMDA-dependent LTP in the neostriatal slices obtained from D₂ receptor knockout mice. Furthermore, under Mg²⁺-free condition, neostriatal slices from wild-type mice induced LTP, and the magnitude of LTP was significantly increased by 1-sulpiride, a D₂ receptor antagonist. On the basis of these observations, it was speculated that activation of D₂ receptors normally exerted a negative control on the induction of NMDA-dependent LTP. We have previously shown that tetanic stimulation with a relatively low frequency (20 Hz, 5 s) produces a long-term enhancement of DA release in the neostriatum and the enhancement involves activation of NMDA receptors. From these observations, we can suggest the following mechanisms for controlling LTP in the neostriatum. In the neostriatum of the naive rats, the long-term enhancement of DA release may activate D₂ receptors and depress NMDA receptor-mediated corticostriatal excitatory inputs. The depression of the NMDA response would inhibit the induction of LTP following tetanic stimulation of the cortex. In EW rats, nigrostriatal DAergic transmission is partially impaired and lost negative D₂ receptor-mediated controls on the expression of LTP, and then strong enhancement of synaptic responses necessary to induce LTP is developed.

The mechanism for the strong transient depression of the amplitude of population spikes induced in the neostriatal slices of EW rats remains unclear. The metabotropic glutamate receptor antagonist, MCPG, partially blocked the transient depression. Although the interactions between NMDA and metabotropic glutamate receptors in neostriatal neurons are still controversial, it can be speculated that metabotropic glutamate receptor activation by tetanic cortical stimulation results in transient depression of the NMDA response and the amplitude of population spikes. The transient depression may act to reduce induction of LTP. The transient depression was totally masked under the Mg²⁺-free condition. Under the Mg²⁺-free condition, fully activated NMDA receptors could surmount the metabotropic glutamate receptor-mediated inhibition and the induction of PTP instead of the transient depression.

CONCLUSIONS

The corticostriatal glutamatergic projections are considered to play major roles in motor and cognitive functions of the basal ganglia. The present study indicates that the neostriatum of naive and EW rats exhibited significant differences in the induction of short- and long-term changes of PSPs and population spikes after tetanic subcortical white matter stimulation. Thus, it may be reasonable to assume that the development of abnormal synaptic plasticities in the neostriatum contributes to EW syndromes. The alternation of tetanic-stimulation-induced changes appears to due to altered NMDA and DAergic transmissions in the neostriatum. The loss of nigrostriatal DA and resultant elevation of NMDA receptor-mediated corticostriatal transmission have been suggested to play a pivotal role in the motor symptoms of Parkinson’s disease. There may be a similar imbalance of two major input systems in the neostriatum of the EW rats.

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