ORIGINAL PAPER

Disturbance of Metabotropic Glutamate Receptor-Mediated Long-Term Depression (mGlu-LTD) of Excitatory Synaptic Transmission in the Rat Hippocampus After Prenatal Immune Challenge

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Abstract

Maternal immune challenge has proved to induce moderate to severe behavioral disabilities in the offspring. Cognitive/behavioral deficits are supported by changes in synaptic plasticity in different brain areas. We have reported previously that prenatal exposure to bacterial LPS could induce inhibition of hippocampal long-term potentiation (LTP) in the CA1 area of the juvenile/adult male offspring associated with spatial learning inabilities. Nevertheless, deficits in plasticity could be observed at earlier stages as shown by the early loss of long-term depression (LTD) in immature animals. Moreover, aberrant forms of plasticity were also evidenced such as the transient occurrence of LTP instead of LTD in 15–25 day-old animals. This switch from LTD to LTP seemed to involve the activation of metabotropic glutamate receptor subtype 1 and 5 (mGlu1/5). We have thus investigated here whether the long-term depression elicited by the direct activation of these receptors (mGlu-LTD) with a selective agonist was also disturbed after prenatal stress. We find that in prenatally stressed rats, mGlu1/5 stimulation elicits long-term potentiation (mGlu-LTP) independently of N-methyl-D-aspartate receptors. Both mGlu5 and mGlu1 receptors are involved in this switch of plasticity. Moreover, this mGlu-LTP is still observed at later developmental stages than previously reported, i.e. after 25 day-old. In addition, increasing synaptic GABA with tiagabine tends to inhibit mGlu-LTP occurrence. By contrast, long-term depression induced with the activation of CB1 cannabinoid receptor is unaffected by prenatal stress. Therefore, prenatal stress drastically alters mGlu1/5-associated plasticity throughout development. MGlu-mediated plasticity is an interesting parameter to probe the long-lasting deficits reported in this model.

Keywords Prenatal stress · Hippocampus · mGlu1/5 · LTD · LTP · Synaptic plasticity · Dihydroxyphenylglycine

Introduction

Uncontrolled infection during pregnancy can increase the risk for the occurrence of neurodevelopmental disease in children, including autism or attention deficit hyperactivity disorder [1–3]. To some extent, rodent models of prenatal immune challenge recapitulate the behavioral deficits observed in the course of these diseases. Exposing dams to bacterial LPS results in the occurrence of cognitive, social, and behavioral deficits in the offspring [4]. Such deficits are reminiscent of 'psychotic-like' conditions in humans. For instance, measurement of prepulse inhibition reflex, a hallmark of 'psychotic-like' estate, demonstrated that prenatal LPS could reduce the effectiveness of this reflex [4]. These cognitive/behavioral deficits are underlined by severe impairments, even loss, of synaptic plasticity as evidenced by the inability to trigger long-term potentiation (LTP) or long-term depression (LTD) of excitatory synaptic transmission in the hippocampi from these animals [5–7]. As we reported previously, these changes may originate from various molecular/cellular mechanisms including a disruption of the excitatory/inhibitory balance. Firstly, we have evidenced a reduction in GABAergic synaptic transmission. Interestingly, reinstating GABA with type 1 GABA transporter (GAT-1) blocker, i.e. tiagabine, restored LTD [8].

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Functional deficits of inhibitory transmission are matched with reduced GABAergic interneuron occurrence in CA3 hippocampal area [8]. Secondly, synaptic NMDA receptor function is decreased after prenatal LPS challenge [7]. In the hippocampus, LTP and LTD are largely dependent on the activation of postsynaptic NMDA receptors [9]. The loss of these phenomena observed in LPS animals is time matched with the decrease of NMDA receptor expression in hippocampal neurons [7]. Nevertheless, the activity of other glutamate receptors may also be disturbed after prenatal stress leading to the occurrence of aberrant forms of synaptic plasticity. This seems to be the case of phospholipase C-coupled metabotropic glutamate receptors (mGlu1/5). Indeed, we observed that a form of LTD induced by paired-pulse afferent stimulation, which involves mGlu1/5 activation [10], was transiently converted into an LTP after prenatal stress. The pharmacological blockade of mGlu1 or mGlu5 receptors leads to the inhibition of this 'aberrant' LTP. By contrast, this 'aberrant' LTP was completely independent of NMDA receptor activation [7].

The direct activation of mGlu1/5 with selective agonist as dihydroxyphenylglycine (DHPG) leads to LTD (mGlu-LTD) in the rodent hippocampus [10–13]. This form of plasticity has received much attention as it is very sensitive to the occurrence of pathological states [13]. Indeed, animal models of multiple brain pathologies, including FMRX-linked mental retardation [14], drug addiction [15, 16], autism [17] are displaying alterations of this form of plasticity. We have thus decided to test whether the mGlu-LTD in the CA1 area of the hippocampus was altered after immune prenatal stress and whether these putative alterations shared similarities with those unveiled for electrically-induced LTD.

Materials and Methods

Drugs

(RS)-3,5-Dihydroxyphenylglycine (DHPG), D-2-amino-5-phosphonovalerate (D-AP5), 2-Methyl-6-(phenylethynyl) pyridine hydrochloride (MPEP), dizolcipine (MK-801), (S)-(+)-α-Amino-4-carboxy-2-methylbenzeneacetic acid (LY 367385) and tiagabine hydrochloride were from Tocris (BioTechne). All other drugs were from Sigma-Aldrich (Merck).

Animal Groups

All experiments were carried out in accordance with the European Community Council Directive of November 24, 1986 (86/609/ECC). This study was approved by the local branch of the 'Comit National de Reflexion Ethique sur l'Experimentation Animale' (CNREEA nu 36) under the

reference CEEA-LR-12099. All efforts were made to minimize animal suffering and to reduce the number of rats used.

Pregnant Sprague–Dawley rats (Centre d'Elevage Depré, St Doulchard, France) were used throughout this study. Animals were housed individually and randomly assigned to either of these experimental groups: (i) a group of control animals born to saline-injected dams (2 ml kg^{-1} ip at the 19th day of gestation GD19) (SAL rats) or (ii) a group of animals born to LPS-treated dams (500 mg kg^{-1} ip at GD19) (LPS rats). LPS (from Escherichia coli, serotype O55:B5) was obtained from Sigma-Aldrich (Saint-Quentin Fallavier, France). After birth, the size of the litters was limited to ten pups. All animals were maintained on a 12-h light/dark cycle with food and water ad libitum.

Electrophysiological Recordings with Micro-electrode Array

Experiments were carried out on hippocampal slices (300 μm thickness) obtained from 11 to 180 day-old male offspring. After decapitation, brains were quickly dissected and placed in ice-cold buffer comprising 124 mM NaCl, 3.5 mM KCl, 25 mM NaHCO$_3$, 1.25 mM NaH$_2$PO$_4$, 1 mM CaCl$_2$, 2 mM MgSO$_4$, 10 mM D-glucose, and 10 mM HEPES (bubbled with O$_2$/CO$_2$, 95/5). Slices were then cut with a Vibratome (VT1000S; Leica, France) and maintained at RT for at least 1 h in the same buffer supplemented with 1 mM CaCl$_2$. This supplemented buffer—also named extracellular medium—was used for further recordings.

For electrophysiological recordings, slices were transferred to a MEA (MEA60; Multi Channel Systems, Reutlingen, Germany) continually superfused with the above described extracellular medium (flow rate 2 ml min^{-1}) and kept at 32 °C. Unless otherwise stated, this medium included AP5 (50 μM) a NMDA receptors selective antagonist. Drugs were directly applied in this superfusion. MEA was positioned on the platform of an inverted microscope (DMLFS, Leica). MEAs comprised 60 extracellular electrodes [6]. The inter-electrode distance was 200 μm. Each individual electrode from the array could be used either as a recording or as a stimulatory electrode. A nylon mesh was positioned above the slice to obtain a satisfactory electrical contact between the surface of the slice and the electrode array. Stimulation was achieved with an external stimulator (STG-1004; Multi Channel Systems) by applying biphasic current pulses to one electrode of the array located in the Schaffer Collateral pathway of the hippocampus. Stimulation intensity (60–300 μA) and duration (70–200 μs) were adapted to avoid multiphasic responses due to an excessive stimulation [18]. Field excitatory postsynaptic potentials (fEPSPs) could then be recorded in the stratum radiatum of the CA1 subfield by all the remaining electrodes of the array at the same time. The fEPSP recorded by the electrodes adjacent to the stimulating

one were used for further analysis (see [19]). Signals were recorded and analyzed (MC Rack; Multi Channel Systems). Baseline synaptic signals were evoked using a 0.066 Hz frequency. Slices displaying epileptic-like activity were discarded. The magnitude of the effects on synaptic transmission was determined by measuring slopes of fEPSPs, which were modified in a similar way to fEPSP amplitudes, as reported by others also using MEA recordings [20]. Data are presented as means ± SEM on graphs plotting pooled data. Each individual ('n') corresponds to an experiment performed on a slice from an individual animal. Pooled data were obtained from animals originating from at least three independent litters in order to avoid possible litter-specific effects.

Statistical Analyses

Statistical analyses were performed using Sigma Stat software. Single curves were analyzed using ANOVA on repeated measures, followed by Holm-Sidak method for multiple comparisons. Curve comparisons were performed using two-way ANOVA, followed by Holm-Sidak method for multiple comparisons. Means of plateau fEPSP amplitudes were compared using ANOVA followed by Fisher LSD method, or t-test when comparing two groups.

Results

In a first set of experiments (Fig. 1), hippocampal slices from rats subjected to prenatal exposure either to saline (SAL-rats) or to LPS (LPS-rats) were treated with DHPG (100 μM). In the age range tested, i.e. 16- to 180-day-old rats, mGlu-LTD (LTD amplitude of $14 \pm 6\%$ of basal) was triggered by DHPG in SAL rats (n = 17). By contrast, an enduring potentiation of excitatory transmission (LTP amplitude of $52 \pm 15\%$ of basal) was observed consistently in LPS rats after DHPG application (n = 19). Therefore, it appears that mGlu-LTD is converted in an 'mGlu-LTP' after prenatal exposure to LPS.

All further experiments were carried out in the presence of AP5 (50 μM), a NMDA receptor antagonist, in order to eliminate NMDA receptor contribution to DHPG-induced actions and thus to evaluate mGlu1/5 receptor-mediated effects more specifically on synaptic transmission. In control animals (SAL, n = 20), mGlu-LTD was substantially lost under NMDA receptor blockade (Fig. 2). In fact when comparing the whole curves obtained either in the presence or the absence of AP5 using two-way ANOVA, we found that a statistical significance could be observed 30 min post DHPG (p = 0.05) which became stronger 40 min after DHPG (p = 0.03). This could be attributable to an increasing
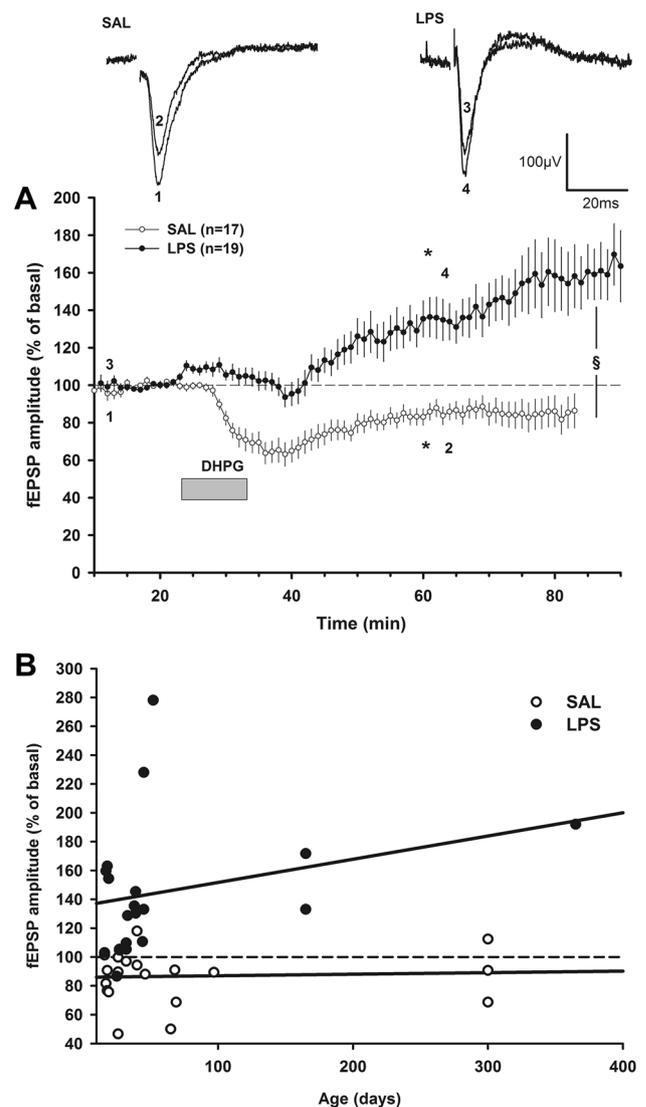

Fig. 1 DHPG-evoked plasticity is altered in LPS-rats. DHPG (100 μM) was applied for 10 min on hippocampal slices from either control (SAL) or LPS rats aged 16 day- to 6 month-old. fEPSP were recorded as described in the material and method section. **a** While a significant long-term depression of fEPSP was observed in SAL rats (n = 17), a significant LTP was induced in LPS rats (n = 19). Sample traces of fEPSP recorded either before (1 and 3) or 30 min (2 and 4) after the application of DHPG, in SAL (1 and 2) or LPS (3 and 4) rats, respectively are shown (top of the graph). *p < 0.05 versus basal fEPSP, using one way ANOVA for repeated measures followed by Holm-Sidak method for multiple comparisons; §p < 0.05 for comparison of LPS versus SAL, using two way ANOVA for repeated measures followed by Holm–Sidak method for multiple comparisons. **b** Developmental profile (from 16 day old to 1 year old) of DHPG-induced plasticity in SAL or LPS rats. Amplitudes of fEPSP were determined either 30 or 35 min following DHPG application for SAL or LPS rats, respectively

recruitment with time of NMDA receptors for the expression of mGlu-LTD.

Fig. 2 D-AP5 prevents the
DHPG- induced LTD in SAL
rats but not the DHPG-induced
LTP in LPS rats. **a** D-AP5
(50 μM) was applied throughout
fEPSP recording of hippocam-
pal slices from either control
(SAL) or LPS rats aged 11 day-
to 3 month-old. Per se D-AP5
did not modify fEPSP ampli-
tude. DHPG was applied for
10 min. #$p < 0.05$ versus basal
fEPSP, using one way ANOVA
for repeated measures fol-
lowed by Holm-Sidak method
for multiple comparisons. *N.S.*
non-significant. §$p < 0.05$ for
comparison of LPS versus
SAL, using two way ANOVA
for repeated measures followed
by Holm–Sidak method for
multiple comparisons. **b** Devel-
opmental profile of DHPG-
induced plasticity in SAL or
LPS rats in the presence of
D-AP5. **c** Summary histogram:
amplitudes of LTD or LTP were
determined on a-15 min plateau
either 30 or 35 min following
the DHPG stimulation for SAL
or LPS rats, respectively. Values
were compared to control
fEPSP baseline using t-test:
**$p < 0.01$; ***$p < 0.001$
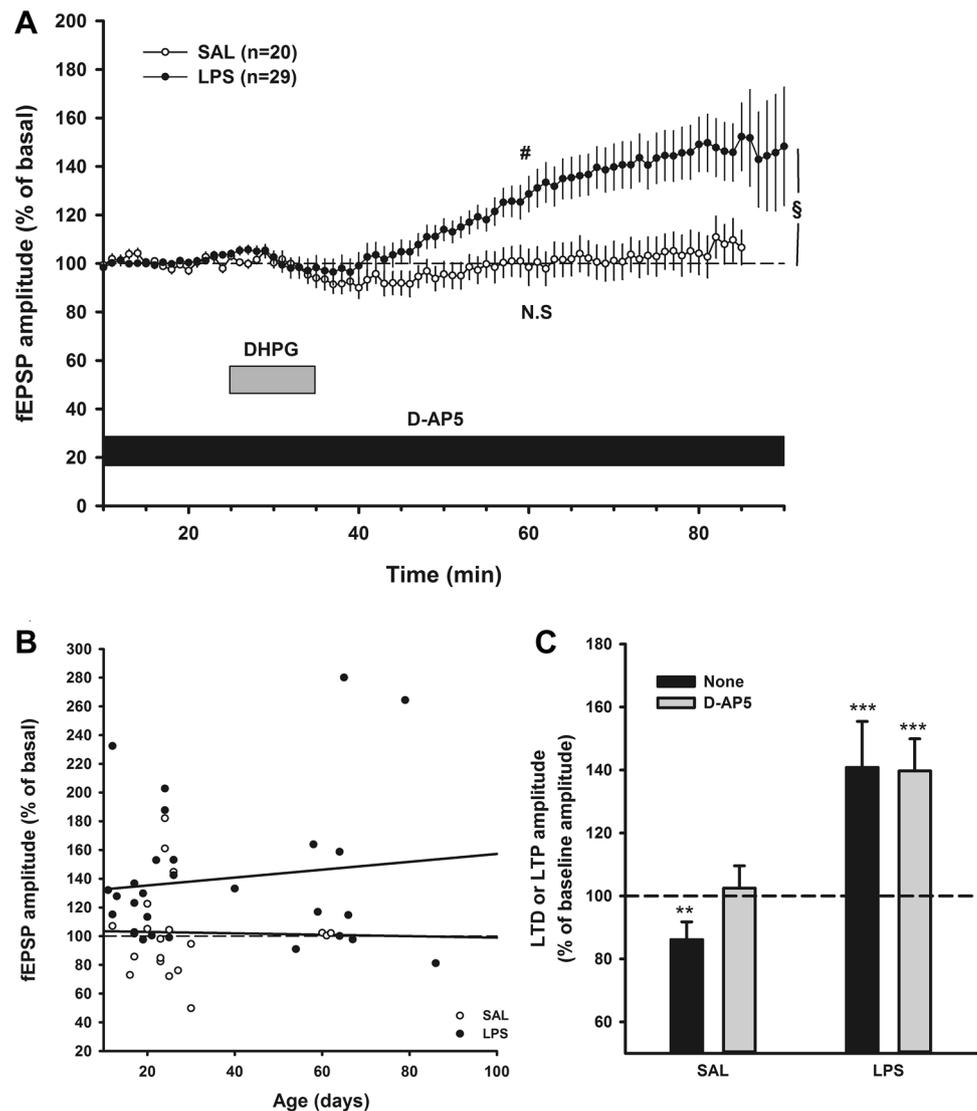
By contrast, mGlu-LTP in LPS animals (n = 29) was com-
pletely insensitive to such application of AP5 (Fig. 2a, b).
When separating data obtained in rats the age range 11- to
25-day-old from those obtained rats older than 25-day-old
(up to 180-day-old), it appears that this DHPG-induced LTP
was consistently observed throughout development (Fig. 3).

The dependence of mGlu-LTD on mGlu1 or mGlu5
activation was further studied in 11–25 day-old SAL rats
with selective antagonists of these receptors i.e. LY367385
(100 μM, n = 7) [21] and MPEP (10 μM, n = 5) [22],
respectively. Both antagonists could block efficiently and
individually the induction of mGlu-LTD (Fig. 4a, b). We
have next examined whether mGlu1 or mGlu5 receptor
blockade could also prevent mGlu-LTP occurrence in LPS
rats. LY367385 (100 μM, n = 9) and MPEP (10 μM, n = 6)
were both able to inhibit mGlu-LTP occurrence (Fig. 5A).
The GAT-1 blocker tiagabine (20 μM, n = 5) was further

tested on the DHPG-induced synaptic plasticity in LPS
animals. Indeed, we have previously demonstrated that
prenatal LPS challenge induced a deficit in the inhibitory
GABA-mediated synaptic transmission [8]. The applica-
tion of tiagabine led to the inhibition of mGlu-LTP occur-
rence in rats subjected to prenatal stress (Fig. 5b).

Finally, we have examined whether the type one can-
nabinoid receptor (CB1R)-associated LTD was also dis-
rupted after prenatal stress. Indeed, CB1R and mGlu1/5
receptor activations are often associated in the regulation
of synaptic plasticity, especially LTD in the hippocam-
pus [23]. The application of the selective CB1R agonist
WIN55,212-2 (10 μM) resulted in a long-lasting synaptic
depression in both SAL and LPS rats. LTD amplitudes
reached 44 ± 6% (n = 7) and 40 ± 8% (n = 5) in SAL and
LPS rats, respectively. These magnitudes of LTD level
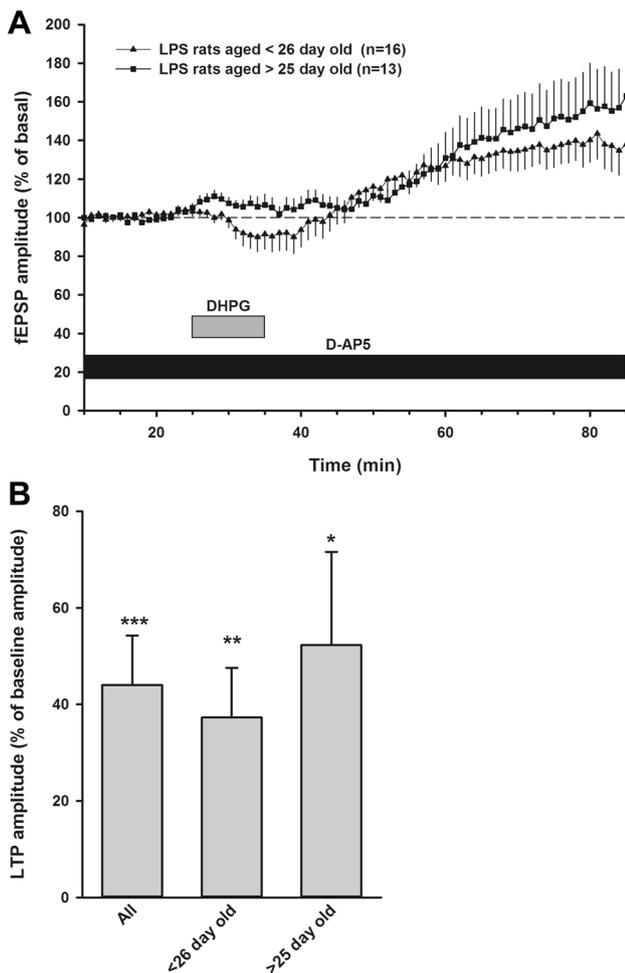were not significantly different from each other (Fig. 6).

Fig. 3 Similar DHPG-induced LTP is observed in LPS rats aged either under or over 25 day old. **a** D-AP5 (50 μM) was applied throughout fEPSP recording of LPS rat hippocampal slices and DHPG was applied for 10 min. Data were separated in two groups according to the age of the animal, i.e. rats aged between 11 and 25 day old (n = 16), and rat aged over 25 day old (n = 13). **b** Amplitudes of LTP were determined on a-15 min plateau, 35 min following the DHPG stimulation. Values were compared to control baseline using t-test: *p < 0.05; **p < 0.01; ***p < 0.001. Comparisons were also performed between the groups using ANOVA followed by Fisher LSD method; any significant difference was observed

Fig. 4 MPEP and LY367385 inhibit the DHPG-induced LTD in SAL rats. **a** Either MPEP (10 μM) or LY367385 (100 μM) was applied 10 min prior to DHPG which was added for a further 10 min on SAL rat hippocampal slices. *p < 0.05 versus basal fEPSP, using one way ANOVA for repeated measures followed by Holm–Sidak method for multiple comparisons; *N.S.* non-significant. §p < 0.05 for comparison of values obtained either in the absence or the presence of antagonist, using two way ANOVA for repeated measures followed by Holm–Sidak method for multiple comparisons. **b** Mean amplitudes of fEPSP were determined on a-15 min plateau, 30 min following the DHPG stimulation. Values were compared to control baseline using t-test: *p < 0.05. Comparison between values obtained either in the absence or the presence of the antagonist was performed using ANOVA followed by Fisher LSD method: #p < 0.05

Discussion

We find here that DHPG-induces an enduring potentiation of the excitatory synaptic transmission in the CA1 area of the hippocampus of rats challenged in utero with LPS. In fact, this form of plasticity, which could be named 'mGlu-LTP', recapitulates the features of the synaptic plasticity induced electrically with paired-pulse low frequency stimuli (so called 'ppulse-LFS-LTP') in these animals [7]. Indeed, we observe that mGlu1/5 activation triggers LTP instead of LTD in LPS rats. This mGlu-LTP occurs independently of NMDA receptor activation, since it is not
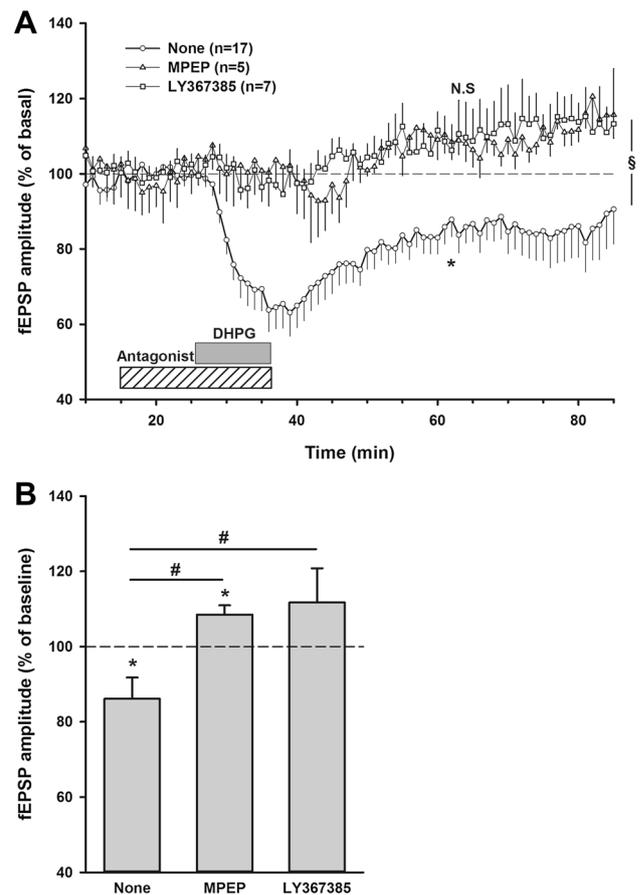
affected by AP5 application. In addition, similar to ppulse-LFS-LTP, it also requires mGlu1 and mGlu5 activation. Therefore, there is a clear dysfunction of the pathways activated by mGlu1/5 in LPS animals as shown by their direct activation by a selective agonist. Nevertheless, there is one noticeable difference in their timing of appearance between mGlu-LTP and the ppulse-LFS-LTP obtained by afferent stimulation: mGlu-LTP in LPS animals lasts over 25 day-old of age while ppulse-LTP was generally extinguished after this age [7]. This suggests that mGlu1/5 dysfunction is enduring but other mechanisms should take place with development to limit mGlu-LTP as revealed by
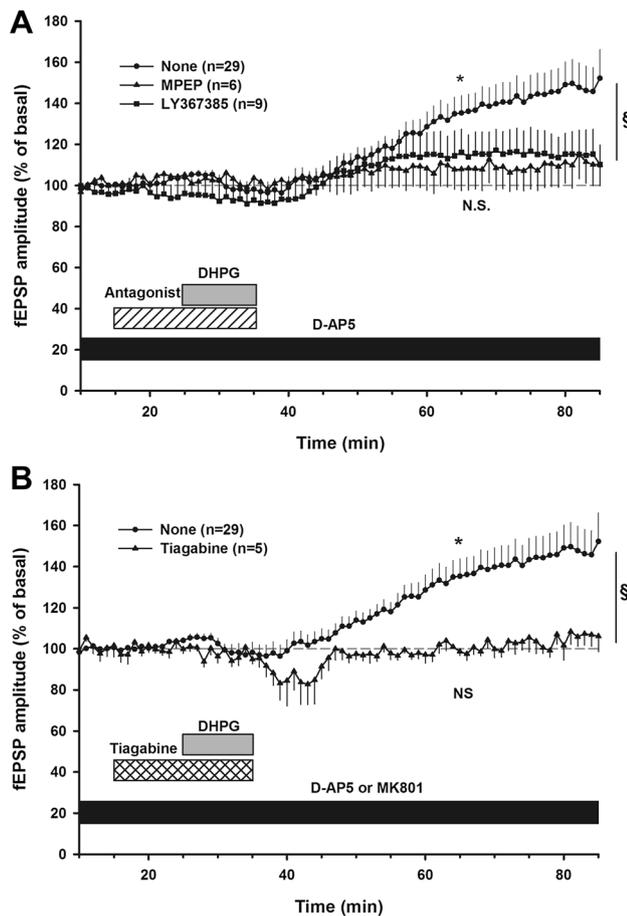
Fig. 6 WIN55-212,2 induces LTD in both SAL and LPS-rats. WIN55-212,2 (10 μM) was applied for 10 min on hippocampal slices from either SAL (n=7) or LPS (n=5) rats. *p < 0.05 versus basal fEPSP, using one way ANOVA followed by Holm–Sidak method for multiple comparisons

Fig. 5 a MPEP and LY367385 inhibit the DHPG-induced LTP in LPS rats in the presence of D-AP5. **a** D-AP5 (50 μM) was applied throughout fEPSP recording of hippocampal slices from LPS rats. MPEP (10 μM) or LY367385 (100 μM) was applied 10 min prior to DHPG which was added for a further 10 min. **b** Tiagabine inhibits the DHPG-induced LTP in LPS rats in the presence of D-AP5 or MK801. D-AP5 (50 μM) or MK801 (10 μM) was applied throughout fEPSP recording of hippocampal slices from LPS rats. Tiagabine (20 μM) was applied 10 min prior to DHPG which was added for a further 10 min. *p < 0.05 *versus* basal fEPSP, using one way ANOVA for repeated measures followed by Holm-Sidak method for multiple comparisons; *NS* non-significant; §p < 0.05 for comparison of recording either in the absence or in the presence of drug, using two way ANOVA followed by Holm–Sidak method for multiple comparisons

the loss of ppulse-LTP induced by electrical stimulation after 25 day-old of age.

There are many molecular mechanisms which could account for the disruption of mGlu-LTD in LPS animals. Our data agree with reduction in GABA-mediated inhibitory transmission and/or in NMDA receptor expression. Firstly, GABA accumulation via GAT-1 blockade with tiagabine inhibits DHPG-induced fEPSP potentiation in LPS rats. This indicates that mGlu-LTP could be partially attributed to a reduced inhibitory transmission, which leads to uncontrolled excitation. We have reported that electrically-induced LTD
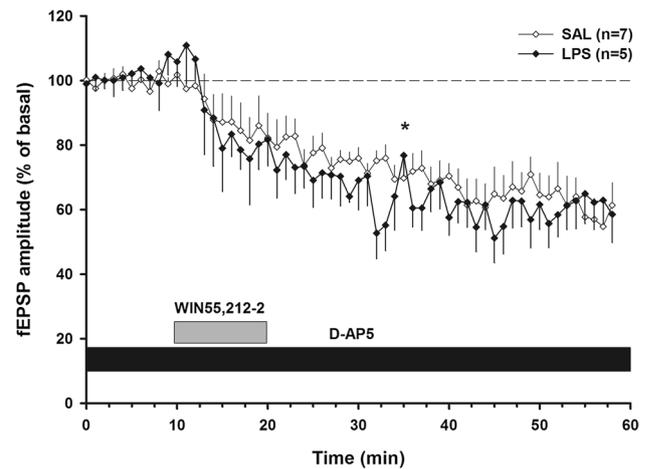
could be rescued in LPS animals by tiagabine [8]. Secondly, the reduction in NMDA receptors at synaptic sites could also be involved in this switch of plasticity. Indeed, blocking NMDA receptors results in the inhibition of mGlu-LTD in SAL animals, while mGlu-LTP is unaffected. Therefore, the presence of NMDA receptors could limit mGlu1/5 receptor activity, as shown previously by interaction studies between NMDA and mGlu5 receptors [24]. The presence of NMDA and mGlu5 receptors at synapses is regulated by intracellular scaffold proteins including Shank and Homer. Moreover, mutations in Shank genes have been associated with forms of autism [25, 26]. Therefore, decreased expression of Shank could also account for the impairment of synaptic plasticity after prenatal stress. Alternatively, disruption of mGlu-LTD could also account for decreased functional interaction with cannabinoid CB1 receptors. Indeed, mGlu5 and CB1R agonists seem to activate common intracellular pathways leading to LTD in the CA1 area of the hippocampus [23]. In our hands, CB1R-mediated LTD appears to be rather unaffected by prenatal exposure to LPS. This suggests that this prenatal stress leads to some rather specific alterations of the mGlu1/5 receptors-associated pathways.

The functional relevance of this switch in synaptic plasticity in LPS animals, i.e. from LTD to LTP, obtained both electrically [7] or through the direct activation of mGlu1/5 remains to be elucidated at the behavioral level. In this line, mGlu1/5 activation is known to contribute to neurophysiological adaptations occurring during several forms of learning. For instance, mGlu5 activation contributes to the LTD evidenced in the hippocampus during spatial object recognition [27]. Therefore, such a switch in plasticity could be deleterious for correct learning acquisition. In support of

this hypothesis, we have reported that spatial learning in the Morris' water-maze was greatly impaired in male rats subjected to such prenatal immune stress [5].

The mGlu-LTD appears to be dysregulated in a wide array of animal models recapitulating mental retardation and autism [17] and drug addiction [12]. It thus provides a robust parameter to probe synaptic deficits. According to the model considered, this form of LTD can be either enhanced or inhibited. Interestingly molecules modulating mGlu5, especially positive allosteric modulators, are exhibiting beneficial effects in alleviating the symptoms observed in different models of psychosis as those obtained by NMDA receptor blockade with MK-801 [28] or by Shank-3 genetic deletion [29]. Therefore, the direct modulation of mGlu1/5 receptors is becoming a promising route in the prospect of curing neurodevelopmental diseases. In addition, the dysfunction of mGlu1/5 receptors could also be attributed to some defects in receptor desensitizing mechanisms involving the GRK/Arrestin pathway. In this line, it has recently been shown that neuroinflammation induced by LPS exposure could sensitize mGlu receptor-associated responses through the downregulation of GRK2 protein [30]. Thus the dysfunction of mGlu1/5 receptors that we observe here after prenatal stress could be due not only to alterations in receptor activation but also to modified mechanisms of receptor trafficking regulation in neurons.

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