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Research article

Chronic but not acute immobilization stress stably enhances hippocampal CA1 metabotropic glutamate receptor dependent Long-Term Depression

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HIGHLIGHTS

- Bath application of DHPG caused robust LTD in hippocampal slices from control animals.
- Chronic immobility stress significantly elevated this LTD when observed 24 h following the last stress event.
- A single stress event did not to enhance LTD, 24 h later.

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ABSTRACT

Acute stress has been shown to facilitate but not increase metabotropic glutamate receptor (mGluR) mediated Long-Term Depression (LTD) in the hippocampus. However, the effect of chronic stress on mGluR dependent LTD has not been investigated. Moreover, whether stress leads to a transient modification LTD threshold or a more stable change in synaptic plasticity needs to be addressed. In the present study, we have explored the effects of both a ten-day long and a single day immobilization stress protocol on mGluR-LTD at the CA3:CA1 synapse in the hippocampus of adult male Sprague-Dawley rats, a day after applying stress. Bath application of the selective group 1 mGluR agonist (*S*)-3,5-dihydroxyphenylglycine (DHPG) promoted robust LTD in hippocampal slices from control (i.e. un-stressed) animals. Administration of immobility stress for two hours per day for ten days significantly elevated this LTD to a level almost twice that of control, when observed 24 h following the last stress event. Acute stress i.e. a single day of two hours of immobilization, however, failed to significantly enhance LTD, 24 h later. These results demonstrate for the first time, that repeated exposure to stress, but not a single stress event, is required to bring about a stable alteration in mGluR mediated synaptic plasticity.

1. Introduction

Stress is known to cause significant structural and functional changes in the hippocampus having important affective and cognitive consequences [1–4]. In this connection various studies have demonstrated that stress enhances long-term depression (LTD), a major form of learning associated synaptic plasticity, in the CA1 region of the hippocampus and this effect is considered to be primarily mediated through the N-methyl-D-aspartate receptor (NMDAR) [5–8]. A solitary study, however, has demonstrated that the facilitatory effect of stress on LTD in the hippocampus also extends to mGluR dependent LTD which is a mechanistically distinct form of plasticity [9]. Interestingly, the mGluRs are considered to play an important role in CNS related diseases such as autism related disorders, pain, neurodegenerative disorders etc. and they constitute important drug targets as well [10–13]. Moreover, recently discovery has been made of small molecules that selectively bind to these receptors highlighting the therapeutic relevance of mGluRs [14]. This prompted us to use (*S*)-3,5-dihydroxyphenylglycine (DHPG), a potent agonist for group 1 mGluRs (both mGluR1 and mGluR5), to chemically induce LTD for assessing the effect of stress on this form of hippocampal synaptic plasticity.

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In previous studies various methods have been employed for eliciting stress which include forced walking [15], elevated platform and foot shock [7], tail shock [8], forced swim [16] restrained stress plus tail shock [17] and only restrained stress [9,18]. In an earlier study we have already demonstrated that the chronic immobility stress protocol followed here can cause dendritic atrophy and disbranching in CA3 pyramidal neurons of the rat hippocampus [2]. The pyramidal cells of the CA3 region form synapses with those in the CA1 region through the Schaffer collateral commissural pathway. Therefore we thought it prudent to investigate the effect of chronic immobility stress on mGluR-LTD in the CA3:CA1 synaptic region in order to find out any functional manifestation of the aforementioned profound morphological changes. In order to ascertain whether the cumulative effect of long term stress is necessary for affecting mGluR-LTD we have used an acute stress model as well, wherein immobility stress was administered only for a single day for 2 h only. Moreover, we have checked the LTD levels a day after the stress regimen is over. This provides a more steady state picture of synaptic plasticity as modified by stress.

Our results show that chronic stress significantly enhances DHPG-LTD at the CA3:CA1 synapse in the rat hippocampus. Acute stress, however, failed to have any significant effect on LTD.

2. Experimental procedures

2.1. Experimental animals

Adult male Sprague Dawley rats have been used for this study. At the beginning of the experiment the animals weighed 250–300 gm and were 6–8 weeks old. Control animals were litter mates of the stress-treated ones. The animals were housed in pairs in HEPA-filtered individually ventilated cages in a standard temperature (22–24 °C) and humidity (30–70%) controlled room with 12 h light and dark cycle (lights on at 7:00A.M.). Food and water were provided ad libitum. All procedures related to animal maintenance and experimentation was done according to CPCSEA approved guidelines (Reg. No. 1068/bc/07/CPCSEA). The study has also been approved by the Institutional Animal Ethics Committee (IAEC).

2.2. Stress protocol

Animals in the 'Chronic Stress' group underwent complete immobilization (2 h/day, 10A.M.–12 P.M.) in rodent immobilization bags without access to either food or water, for 10 consecutive days [2]. Rats belonging to the 'Acute Stress' group were subjected to immobilization only once for 2 h. Control animals were not subjected to any type of stress. All the animals were allowed a 24 h recovery period before sacrifice. The following additional parameter was measured in order to monitor the overall effect of the stress regimen: percentage change in body weight i.e. net change in weight after experiment × 100/weight at the beginning of experiment.

2.3. Hippocampal slice preparation and electrophysiology

Twenty four hours after stress, the animals were sacrificed by decapitation under deep anesthesia using halothane. The brain was quickly removed and immersed for 1 min in an ice-cold cutting solution containing (in mM): 60 NaCl, 3 KCl, 28 $NaHCO_3$, 5 glucose, 1.2 NaH_2PO_4, 7 $MgCl_2$, 0.5 $CaCl_2$, 110 Sucrose, 0.6 Na-ascorbate under constant saturation with carbogen (95% O_2/5% CO_2). The hippocampi were carefully extracted and 400 μM thick transverse slices were prepared in the horizontal plane using McIlwain tissue chopper (Mickle Laboratory Engineering Co Ltd., Surrey, UK). The slices were collected in a holding chamber in artificial CSF (ACSF) containing (in mM): 118 NaCl, 2.5 KCl, 25 $NaHCO_3$, 10 glucose, 1.2 NaH_2PO_4, 1.3 $MgCl_2$, 2.5 $CaCl_2$, where they were allowed to recover for 1–1.5 h at 30 °C in ACSF saturated with carbogen. Following recovery the slices were placed in the recording chamber, where they were continuously perfused with carbogenated ACSF (flow rate of 2 ml/min) at room temperature (22–24 °C).

Synaptic responses were evoked by stimulating the Schaffer collateral pathway (emanating from the CA3 region) using a bipolar platinum-iridium electrode (FHC, Maine, USA). The extracellular recording electrode was made of glass micropipette filled with ACSF and placed in the stratum radiatum of the CA1 region. Extracellular field excitatory post synaptic potential (fEPSP) slope value was recorded using a LTP software (WinLTP, [19]). A test pulse (single current pulse of 100 μs duration at 0.033 Hz) was delivered to evoke a fEPSP. Once a response was evoked, the stimulus intensity was gradually increased to generate an Input/Output (I/O) curve until a population spike was generated. The stimulus intensity was then decreased until it evoked 50–60% of the maximal response and this intensity was used for generating a stable baseline for the whole experiment. The evoked responses were amplified using a high-impedance differential AC amplifier (A-M Systems, Washington, USA) and digitized at 10 kHz A/D rate (National Instruments, USA). Once a stable baseline is obtained DHPG (50 μM) was bath applied for 15 min and its effect on fEPSPs was monitored for 55 min following the onset of its application [9]. In the text percentage LTD refers to the percentage reduction in the fEPSP slope values during the last 5 min of the washout period compared to that during the 5 min period just preceding DHPG application.

2.4. Chemicals

(*S*)-3,5-Dihydroxyphenylglycine (DHPG) was obtained from Tocris Bioscience (Missouri, USA). All other chemicals were procured from Sigma-Aldrich (USA). Fresh stock of DHPG was prepared every week.

2.5. Statistics

All data, presented as mean ± SEM, were compared by means of Student's *t* tests (two-group comparisons) and ANOVA's with/without repeated measures, followed, if significant, by Tukey's multiple comparison tests. In all tests, the significance level was preset to $p < 0.01$.

3. Results

3.1. Chronic Stress enhances mGluR-LTD

In order to find out whether Chronic Stress has any effect on mGluR mediated LTD the animals were made to undergo a two hour/day immobility stress regimen for 10 days as shown schematically in Fig. 1A. Twenty four hours after the last day of stress the animals were sacrificed and hippocampal slices were prepared. Bath application of DHPG (50 μM for 15 min) in control slices caused an initial depression in excitatory synaptic transmission which was followed by 22.8 ± 2.9% LTD (Mean ± SEM, n = 16) in the last 5 min of the washout period (Fig. 1B). In slices of animals that underwent Chronic Stress the initial depression in excitatory synaptic transmission was similar to that in control slices but the level of LTD was enhanced almost two fold to 44.3 ± 3.5% (Mean ± SEM, n = 16) during the last 5 min of the washout period (Fig. 1B). Fig. 1C compares the mean LTD values for control and stressed animals.

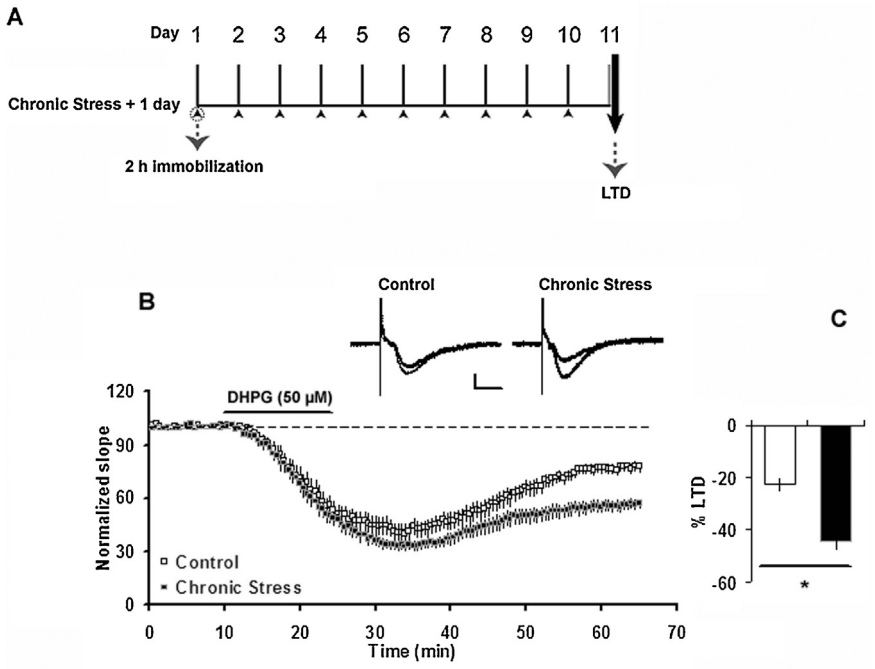

Fig. 1. Chronic Stress enhances mGluR-LTD in hippocampal area CA1.
A: Schematic showing the Chronic Stress protocol. Control animals were not exposed to any stress.
B: Bath application of 50 μM DHPG for 15 min induced significantly more LTD in slices from stressed animals in comparison to those from control animals.
C: Mean ± SEM values of percentage LTD. Percentage LTD refers to the percentage reduction in the normalized fEPSP slope values during the last 5 min of the washout period compared to the 5 min period preceding DHPG application. * $p < 0.01$, Control (n = 16) and Chronic Stress (n = 16). Scale bars: 0.2 mV, 10 ms.

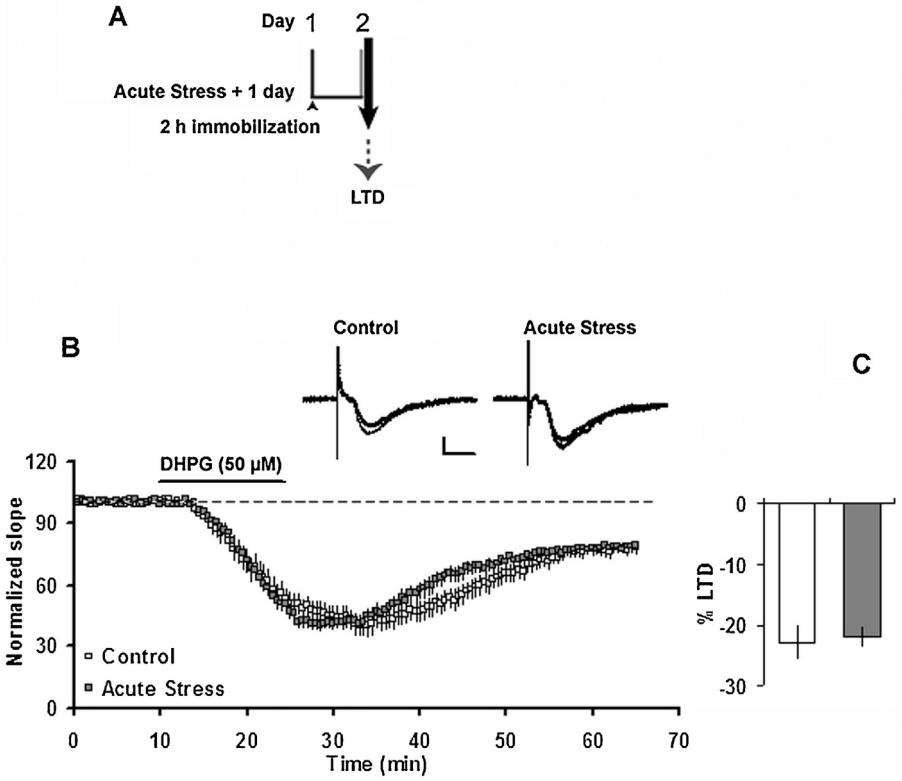

Fig. 2. Acute Stress fails to enhance mGluR-LTD in hippocampal area CA1.
A: Schematic showing the Acute Stress protocol. Control animals were not exposed to any stress.
B: DHPG does not elicit greater LTD in slices from animals which underwent one day stress in comparison to those from control animals.
C: Mean ± SEM values of percentage LTD. Percentage LTD refers to the percentage reduction in the normalized fEPSP slope values during the last 5 min of the washout period compared to the 5 min period preceding DHPG application. Acute Stress (n = 12) and Control (n = 16). Scale bars: 0.2 mV, 10 ms.

3.2. Acute Stress fails to enhance mGluR-LTD

In order to ascertain whether Acute Stress has any effect on mGluR-LTD we exposed the animals to immobility stress for two hours only once. Twenty four hours later the animals were sacrificed and hippocampal slices were prepared (Fig. 2A). In these animals DHPG induced LTD was found to be 21.9 ± 1.8% (Mean ± SEM, n = 12) which was not significantly different from that in control animals (Fig. 2B & C).

3.3. Effect on body weight

To compare the indices of alteration in LTD with other generalized effects of Chronic Stress we have monitored the relative change in the body weight in the experimental animals. Percentage change in body weight was significantly ($p > 0.001$; Student's *t* test) reduced after completion of the 10 days of the stress protocol (Chronic Stress: −0.93 ± 0.9%, 34, n = 10; Control: +7.42 ± 1.86%, n = 8).

4. Discussion

The present study demonstrates for the first time that chronic immobility stress significantly enhances mGluR mediated DHPG induced LTD in the hippocampal CA1 region of SD rats twenty four hours following the stress regimen, whereas acute stress fails to do so when checked 24 h after a single stress event. Previous studies have shown that stress has a facilitatory effect on NMDAR mediated LTD [5–8,20,21]. But mGluR-LTD uses a distinctly alternate mechanism of synaptic plasticity [22] and in recent times mGluR mediated modification of synaptic efficiency is considered to have important implications in neurological disorders [23]. In this regard the effect of both chronic and acute stress on this alternate form of LTD warrants careful consideration.

In 2007, Chaouloff et al. demonstrated for the first time that acute stress lowers the threshold of mGluR-LTD[9] and in a subsequent study they showed that this effect can be mimicked by brief application of corticosterone [24]. Interesting differences, however, exist between their earlier study and our findings. Firstly, they had found that 50 μM DHPG was not effective in causing LTD in control slices but only in acutely stressed ones, and while 100 μM of DHPG was successful in eliciting LTD in control slices, this was not further enhanced by stress. This might indicate that the stress protocol employed by Chaouloff et al. [9], viz. 30 min of restraint followed by 90 min of recovery, only lowered the threshold for LTD without affecting its efficiency. In contrast to this, we have observed that bath application of 50 μM of DHPG for 15 min was effective in causing a robust LTD in control slices which was further enhanced almost two times by Chronic Stress. Our results agree with earlier reports showing that 50 μM of DHPG is efficient in causing significant LTD in control slices [25,26]. Interestingly, Chaouloff et al., reported that when control slices were given longer rest they displayed LTD with 50 μM DHPG itself [9]. Secondly, we have observed that a single stress event could not elicit a stable enhancement of mGluR.-LTD. In view of this it may be stated that stress effect as observed by Chaouloff et al., [9] might have been a transitory feature and chronic exposure to stress is necessary for effecting a stable modification of synaptic efficacy. In terms of methodology, Chaouloff et al., provided a cut between the CA3 and CA1 regions to prevent epileptic activity and also used picrotoxin throughout the experiment to block inhibitory transmission. Since it has been reported that epileptic activity does not specifically affect DHPG induced LTD [27] we did not apply this modification in our study. Secondly, while it is known that picrotoxin enhances this form of LTD [28], we thought it prudent not to employ such treatments in order to avoid any extraneous factors another than stress to act on the tissue especially since we were getting robust LTD even from unstressed slices.

Several studies have delineated the central role played by stress induced corticosterone release in modulating hippocampal synaptic plasticity [9,24,29,30]. In a previous study, our group had shown that serum corticosterone levels remain significantly high at 24 h following both chronic and acute stress [31] i.e. at the time point when we did our recordings. Since our findings show that acute stress fails to enhance LTD at a time point when circulating corticosterone should be significantly high, this might suggest that sustained and not a shorter exposure to heightened corticosterone concentration is necessary for stably increasing the efficiency of DHPG mediated mGluR-LTD. Chronic exposure to high corticosterone level has indeed been shown to produce hippocampal atrophy, hamper memory formation and cause deleterious structural alterations in the hippocampus of rodent brains [32–34], while an acute exposure does not have such effects [32,33]. Interestingly, a recent study has demonstrated that the serotonin reuptake inhibitor, fluoxetine can abrogate LTD induced in a behavioral stress model [35]. Although this study is focused on NMDAR-LTD, future work can investigate the role of relevant neurotransmitters and their regulations in modulating mGluR-LTD.

In a previous study we have demonstrated that Chronic Stress causes profound structural remodeling in the CA3 pyramidal neurons including atrophy of apical and basal dendrites of the CA3 pyramidal cells [2]. As these cells form synapses with the CA1 neurons via the Schaffer collateral commissural pathway, therefore it is reasonable to assume that the observed changes in LTD at the CA1 neurons could be one functional outcome of the altered CA3 pyramidal neurons. It is relevant to note here that possibility of involvement of pre-synaptic neurons in mediating mGluR-LTD has been suggested by several authors. For example, involvement of DHPG-LTD in altering paired pulse facilitation [36–39] and decreasing neurotransmitter release [40] point to the possibililty of pre-synaptic neurons being a possible locus of DHPG induced mGluR-LTD.

Taken together, these data demonstrate for the first time, that repeated/chronic exposure to stress, rather than a single stressful experience is necessary to bring about long lasting alteration in hippocampal synaptic plasticity. There is now ample evidence to show prolonged stress leads to cognitive and mood disorders, and adversely impacts even neurodegenerative disorders such as Alzheimer's and Parkinson's diseases [41]. The mGluRs are found in diverse cell types in the central and peripheral nervous system and have multifarious effects in their physiology and disease [10,42]. Thus considering the important therapeutic utility of mGluRs future experiments should concentrate on the usefulness of this target in mitigating the detrimental effects of long-term stress.

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