Neurobiology of Learning and Memory xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Different mechanisms underlie stress-induced changes in plasticity and metaplasticity in the prefrontal cortex of juvenile and adult animals Emotional-induced metaplasticity in the prefrontal cortex

Tala Khazen[a,1], Kuldeep Shrivastava[a,1], Reem Jada[a], Ossama A. Hatoum[b], Mouna Maroun[a,*]

[a] Sagol Department of Neurobiology, Faculty of Natural Sciences, University of Haifa, Haifa 3498838, Israel
[b] Department of Surgery B- HaEmek Medical Center, Faculty of Medicine, Technion: Israel Institute of Technology, Afula Israel

ARTICLE INFO

Keywords:
Subiculum
LTP
MK801
Stress

ABSTRACT

Metaplasticity is the dynamic regulation of the ability to induce activity-dependent synaptic plasticity and is governed by the prior history of the synapses. Previous reports by others and us have shown that behavioral stress induces a form of emotional metaplasticity that affects the ability to induce LTP in the subiculum–medial prefrontal cortex pathway, which depends on NMDA receptors (NMDAr). However, studies addressing the effects of stress on LTP and metaplasticity have mainly focused on the adult animal. Here we compared the effects of exposure to stress on the induction of LTP in adult and juvenile animals and examined whether a low dose of NMDAr antagonist (MK801) that does not affect LTP *per se* would differentially affect stress-induced metaplasticity in adult and juvenile animals.

Our findings show that exposure to the elevated platform differentially affects the induction of LTP in adult and juvenile animals. Specifically, whereas exposure to stress resulted in impaired LTP in adult animals, it resulted in enhanced LTP in juvenile animals. Similarly, while MK801 failed to inhibit the induction of LTP in both age groups, it resulted in inhibition of stress-induced enhanced LTP in juvenile animals, but did not affect stress-induced impaired LTP in adult animals. Taken together, these findings demonstrate that emotional metaplasticity is differently dependent on NMDAr in adult and juvenile animals that may stem from developmental differences in the NMDA receptor representation. These results further confirm that the mechanisms of plasticity following stress are distinctive in the two groups of age.

1. Introduction

The term “metaplasticity” refers to the modulation of the ability to induce synaptic plasticity in the form of long-term potentiation (LTP) or long-term-depression (LTD) following prior activation of the synapses (Richter-Levin & Maroun, 2010; Schmidt, Abraham, Maroun, Stork, & Richter-Levin, 2013). Essentially, metaplasticity entails a change in the physiological or biochemical state of neurons or synapses that alters their ability to generate synaptic plasticity (Abraham, 2008). Exposure to stress has been suggested to induce behavioral metaplasticity affecting the induction of plasticity in the CA1 subregion of the hippocampus (Abraham & Tate, 1997; Foy, Stanton, Levine, & Thompson, 1987; Kim & Yoon, 1998; Maroun & Richter-Levin, 2003; Xu, Anwyl, & Rowan, 1997).

The ventral hippocampus/subiculum innervates the medial prefrontal cortex (mPFC), and constitutes the major monosynaptic unidirectional projection between the hippocampus and the mPFC regions (Godsil, Kiss, Spedding, & Jay, 2013; Öngür & Price, 2000). The hippocampus and mPFC exhibit increased synchrony in anxiogenic environments (Adhikari, Topiwala, & Gordon, 2010; Schoenfeld et al., 2014). Both mPFC and hippocampus are enriched in glucocorticoid receptors and they play a role in modulating activity of the hypothalamic-pituitaryadrenal (HPA) axis (Avital, Segal, & Richter-Levin, 2006). The hippocampus and the prefrontal cortex are sensitive to stress as both are targets for the action of glucocorticoids that mediate the effects of stress on emotions and cognition (for example, Xu et al., 1997). Similar to the effects of stress on CA1-LTP, previous studies including ours have shown that exposure to stress inhibits the ability to induce LTP in the subiculum-mPFC pathway (Richter-Levin & Maroun, 2010; Rocher, Spedding, Munoz, & Jay, 2004). Interestingly, we have found that LTP in the subiculum-mPFC is also regulated by metaplastic effects involving electrical activation of the basolateral amygdala (BLA)

* Corresponding author.
E-mail addresses: mmaroun@psy.haifa.ac.il, mouna.maroun@gmail.com (M. Maroun).
[1] Authors equally contributed to this work.

https://doi.org/10.1016/j.nlm.2018.02.011
Received 14 September 2017; Received in revised form 1 February 2018; Accepted 9 February 2018

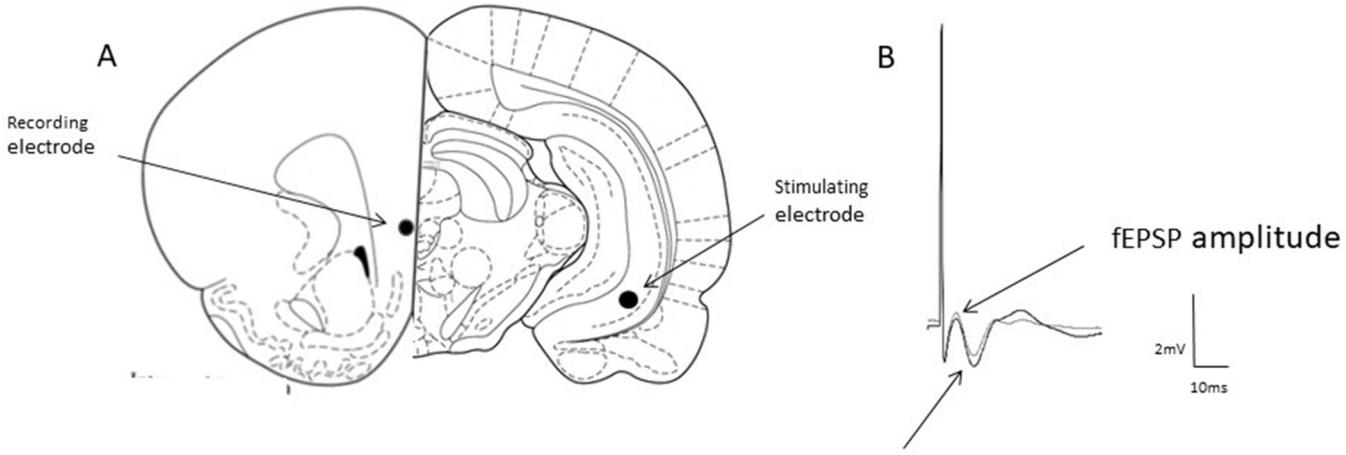

Fig. 1. A: Placement of the recording and stimulating electrodes in the mPFC and the ventral hippocampus, respectively. A diagram depicting a coronal section of the rat brain showing electrode placements in the mPFC and ventral hippocampus. B: fPSP signal that is recorded from the Sub-mPFC pathway. Arrows indicate the peak to peak measurements.

that is reciprocally connected with the mPFC (Maroun & Richter-Levin, 2003; Vouimba & Maroun, 2011). Specifically, electrical activation of the BLA prior to the application of high frequency stimulation to the subiculum mimicked the effects of exposure to stress, resulting in impaired LTP in the mPFC (Richter-Levin & Maroun, 2010).

Metaplasticity depends on NMDA receptors, as the blockade of NMDA receptors by the NMDAr antagonist MK801 at a dose that does not affect LTP *per se* (Rosenblum, Maroun, & Richter-Levin, 1999) affected the plasticity that was induced by stress or BLA activation and diminished the effects on the induction of LTP (Richter-Levin & Maroun, 2010). Metaplasticity and the mechanisms of stress modulation of plasticity have been mainly addressed in adult animals. However, we have recently shown that stress has different impact on BLA–prefrontal cortex LTP in adult and juvenile animals (Maroun & Richter-Levin, 2003; Schayek & Maroun, 2014).

Juvenility is a transitional developmental stage during which the mPFC, the hippocampus, and their projections continue to mature (Giedd, 2015; Schayek & Maroun, 2014; Tottenham & Sheridan, 2009). Further, critical changes in interneurons and in the balance between dopaminergic and glutamatergic neurons occur at juvenility (Benes, 2000; Brake, Sullivan, & Gratton, 2000; Sullivan & Gratton, 2002; Tarazi & Baldessarini, 2000). In particular, the NMDA receptor subunits representation is not the same across the lifespan (Haberny et al., 2002; Winslow, Insel, Trullas, & Skolnick, 1990; Yashiro & Philpot, 2008). Thus, based on these developmental differences we sought in the present work to address possible differences between adult and juvenile animals in the mechanisms of metaplasticity in the mPFC. To that end, we addressed the effects of exposure to stress on LTP induction in the subiculum-mPFC pathway and the role of NMDA receptors in mediating these effects by their blockade with MK801 at a dose that does not affect the induction of LTP *per se* but may affect the metaplasticity induced by exposure to stress.

We show differential effects of stress on prefrontal cortex LTP, consistent with our previous findings. In addition, we show that exposure to behavioral stress induces a form of metaplasticity that is differentially dependent on NMDA receptors in adult and juvenile animals.

2. Materials and methods

2.1. Animals

The experiments were performed using adult (~60 days old) and juvenile (25–27 days old) male Sprague Dawley rats from the local animal colony at the University of Haifa. Only 1–2 animals were taken from each litter to control for litter effects. Pups were separated from the dam at the age of 21 days and housed in Plexiglas cages (4–5 rats per cage). Animals were maintained on a free-feeding regimen and a 12 h light to 12 h dark schedule. All procedures were performed in strict accordance with University of Haifa animal welfare regulations and National Institutes of Health Guidelines for the Care and Use of Laboratory Animals (NIH publication number 8023).

2.2. Behavioral stress protocol

Stress was evoked by placing the rats on an elevated platform (12 × 12 cm) in a brightly lit room for 30 min (Maroun & Richter-Levin, 2003; Schayek & Maroun, 2017; Xu et al., 1997). After the termination of the stressor, rats were immediately anesthetized and taken for electrophysiological testing.

2.3. Electrophysiology

2.3.1. Surgery

Adult and juvenile male Sprague Dawley rats were anesthetized (with 40% urethane, 5% chloral hydrate in saline; 0.5 ml/100 g, i.p.) and placed in a stereotaxic frame (Stoelting, USA) with body temperature maintained at 37 ± 0.5 °C. In brief, small holes were drilled into the skull to allow the insertion of electrodes into the brain. A single recording microelectrode (glass; tip diameter of 2–5 μm; filled with 2 M NaCl; resistance of 1–4 MΩ) was slowly lowered into the ipsilateral mPFC (Adults: anteroposterior, 3.0–3.3 mm anterior to bregma; 0.7–1.0 mm lateral; 3.8–4.8 mm below pial surface. Juveniles: anteroposterior, 2.7 mm anterior to bregma; 0.6 mm lateral; 3.4–3.8 mm below pial surface; Fig. 1).

A bipolar 125 μm stimulating electrode was implanted in the area of the CA1/subicular region of the ventral hippocampus (Adults: 6.3–6.8 posterior to bregma; 5.5 lateral; 4.0–5.8 mm below pial surface. Juveniles: 5.4 posterior to bregma; 4.8 lateral; 6–7.5 mm below pial surface). The evoked responses were digitized (10 kHz) and analyzed using the Cambridge Electronic Design (Cambridge, UK) 1401 + and its Spike2 software. Offline measurements were made of the amplitude of field post-synaptic potentials (fPSPs), using averages of five successive responses to a given stimulation intensity applied at 0.1 Hz. Test stimuli (monopolar pulses; 100 μs duration) were delivered at 0.1 Hz. After positioning the electrodes, the rats were left for 30 min before commencing the experiment. Postsynaptic potential amplitudes were expressed as a percentage change of the baseline (Gurden, Takita, & Jay, 2000; Jay, Burette, & Laroche, 1995).

2.3.2. LTP induction

Theta Burst Stimulation protocols (TBS): In adult animals, we used