



Impact of Maternal Separation on Long-Term Potentiation: Insights from Rodent Models

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Authors

Fateme Pishgooei
Saeid Mehrazin
Khadijeh Esmaeilpour*

Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

*Corresponding author:

Khadijeh Esmaeilpour,
Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
esmaeilpour@kmu.ac.ir

ABSTRACT

Maternal separation (MS) is a well-characterized model of early life stress, based on the postnatal disruption of the mother-infant interaction. Studies on rodents have demonstrated that MS, as an early adverse life event, leads to spatial memory deficits and lasting changes in brain plasticity. Here, we review data from animal studies regarding the impact of MS on long-term potentiation (LTP). Evidence shows that animal models are useful for evaluating the effects of MS on LTP. Overall, studies suggest that MS impairs LTP.

Keywords: maternal separation, long term potentiation, rodent model

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INTRODUCTION

Mother-infant interactions significantly influence the development of physiology and behavior during the first weeks after birth. Since rodent pups are completely dependent on their mothers during the first three weeks of life, separation from their dams is particularly stressful at that time (1). Brain plasticity is highly vulnerable to stress, and the early postnatal period is critical for the development of normal brain function (2). During the first weeks after birth, there is an increase in the proliferation, differentiation, and migration of neurons. Neurogenesis of hippocampal granule cells peaks in the second week of rodent life and during the third month in humans (3).

Electrophysiological studies have been conducted to uncover the cellular basis of the reduction in learning and memory functions in

rats that experienced early-life stress. Specifically, LTP was evaluated because hippocampal LTP is widely considered a putative mechanism of memory storage and has proven to be a valuable model for studying neuronal plasticity at the cellular level (4-7). Stress affects hippocampal LTP (8), and exposure to glucocorticoids reduces hippocampal LTP (9). In this mini review, we will focus on the effects of MS on LTP.

MS as an animal model

MS has been proposed as a well-established animal model of early life stress (10-12). The MS method involves the repeated separation of rodent pups from their dam for either short periods (less than 60 minutes) or prolonged periods (more than 180 minutes) during the first 2-3 weeks of life (13). Short MS simulates naturalistic conditions,

whereas prolonged MS is considered a risk environment (14-16).

Effect of MS on LTP in adolescence

Adolescence is the final stage in a series of neurodevelopmental phases during which synaptic balance and stabilization are achieved, and cognitive function and synaptic plasticity mature (17). The timing and duration of early life stress are crucial for the proper organization of neurons and can increase the risk of developing lasting behavioral disorders (18).

In our previous study, we demonstrated that separating female pups from their mother for 3 hours daily from postnatal day (PND) 1 to 14 impairs LTP induction in the CA1 area of the hippocampus during adolescence (19). Another study found that separating litters from their dams for 4 hours per day from PND 2 to PND 20 reduced the magnitude of LTP at the mossy fiber-CA3 synapse (20). Cao et al. revealed that both the EPSP slope and PS amplitude were reduced in maternally separated male rats (21). According to Gruss et al., a single 24-hour MS episode at PND 9 prevents LTP reinforcement induced by swim stress in adolescent male rats (22). Another study evaluating the effect of MS on LTP in the medial prefrontal cortex (mPFC) of adolescent rats showed that MS induced impairment in LTP (23). Additionally, it was found that the magnitude of hippocampal LTP at CA3-CA1 synapses induced by PBS stimulation was significantly lower in MS animals during adolescence compared to controls. In this study, animals underwent MS for 180 minutes per day from PND 1 to 2 (24-25).

Effect of MS on LTP in adulthood

Some experiments have demonstrated that MS causes alterations in synaptic plasticity extending into adulthood. Xiong et al. found that adult female rats subjected to MS from postnatal day (PND) 2 to 14 exhibited significant LTP impairment in both the infralimbic prefrontal cortex and hippocampal SC-CA1 pathways (26). Herpfer et al. reported that LTP was impaired in adult mice following early deprivation from PND 1 to PND 14 (27). Another research group observed that senescent MS animals exhibited a lower magnitude of hippocampal LTP. These results support the hypothesis that the neuronal and endocrine alterations induced by early-life

stress are long-lasting and can exacerbate the mild age-associated deficits observed in normal aging animals (28). Guo et al. demonstrated that in vivo LTP induced by high-frequency stimulation (HFS) at hippocampal SC-CA1 synapses was suppressed in rats with neonatal MS (29).

The underlying mechanisms for the impairment of functional synaptic plasticity in the mPFC and hippocampus are likely complex. Factors may include a reduction in dendritic complexity and spine density (30, 31), apoptosis of pyramidal neurons in the dentate gyrus region (32), and a reduction in the expression of hippocampal brain-derived neurotrophic factor (BDNF) levels and NMDA receptor subunits (33, 34).

Most studies on the effect of MS in rats or mice have concluded that maternal care is crucial for brain development. Consequently, its absence, even if transient, has been proposed to disrupt maturational processes, ultimately impairing synaptic long-term potentiation in the medial PFC and hippocampus of adolescent and adult MS rats.

DECLARATIONS

Authors have no conflict of interest to declare.

REFERENCES

- [1] Sanchez MM, Ladd CO, Plotsky PM. Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. *Development and psychopathology*. 2001;13(3):419-49.
- [2] Neigh G, Ritschel L, Kilpela L, Harrell C, Bourke C. Translational reciprocity: Bridging the gap between preclinical studies and clinical treatment of stress effects on the adolescent brain. *Neuroscience*. 2013;249:139-53.
- [3] Seress L, Abraham H, Tornoczky T, Kosztolányi G. Cell formation in the human hippocampal formation from mid-gestation to the late postnatal period. *Neuroscience*. 2001;105(4):831-43.
- [4] Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*. 1993;361(6407):31.
- [5] Andersen P, Sundberg S, Sveen O, Swann J, Wigström H. Possible mechanisms for long-lasting potentiation of synaptic transmission in

- hippocampal slices from guinea-pigs. *The Journal of Physiology*. 1980;302(1):463-82.
- [6] Alger B, Teyler T. Long-term and short-term plasticity in the CA1, CA3, and dentate regions of the rat hippocampal slice. *Brain research*. 1976;110(3):463-80.
- [7] Silva AJ. Molecular and cellular cognitive studies of the role of synaptic plasticity in memory. *Journal of neurobiology*. 2003;54(1):224-37.
- [8] Foy MR, Stanton ME, Levine S, Thompson RF. Behavioral stress impairs long-term potentiation in rodent hippocampus. *Behavioral and neural biology*. 1987;48(1):138-49.
- [9] McEwen BS. Stress and hippocampal plasticity. *Annual review of neuroscience*. 1999;22(1):105-22.
- [10] Kalinichev M, Easterling KW, Plotsky PM, Holtzman SG. Long-lasting changes in stress-induced corticosterone response and anxiety-like behaviors as a consequence of neonatal maternal separation in Long-Evans rats. *Pharmacology Biochemistry and Behavior*. 2002;73(1):131-40.
- [11] Francis DD, Diorio J, Plotsky PM, Meaney MJ. Environmental enrichment reverses the effects of maternal separation on stress reactivity. *Journal of Neuroscience*. 2002;22(18):7840-3.
- [12] Romeo RD, Mueller A, Sisti HM, Ogawa S, McEwen BS, Brake WG. Anxiety and fear behaviors in adult male and female C57BL/6 mice are modulated by maternal separation. *Hormones and behavior*. 2003;43(5):561-7.
- [13] Pryce CR, Rüedi-Bettschen D, Dettling AC, Weston A, Russig H, Ferger B, et al. Long-term effects of early-life environmental manipulations in rodents and primates: potential animal models in depression research. *Neuroscience & Biobehavioral Reviews*. 2005;29(4-5):649-74.
- [14] Lehmann J, Feldon J. Long-term biobehavioral effects of maternal separation in the rat: consistent or confusing? *Reviews in the neurosciences*. 2000;11(4):383-408.
- [15] Nylander I, Roman E. Is the rodent maternal separation model a valid and effective model for studies on the early-life impact on ethanol consumption? *Psychopharmacology*. 2013;229(4):555-69.
- [16] Vetulani J. Early maternal separation: a rodent model of depression and a prevailing human condition. *Pharmacological reports*. 2013;65(6):1451-61.
- [17] Selemon LD. A role for synaptic plasticity in the adolescent development of executive function. *Translational psychiatry*. 2013;3(3):e238.
- [18] Biggio F, Pisu M, Garau A, Boero G, Locci V, Mostallino M, et al. Maternal separation attenuates the effect of adolescent social isolation on HPA axis responsiveness in adult rats. *European Neuropsychopharmacology*. 2014;24(7):1152-61.
- [19] heydari A, Esmaeilpour K, Sheibani V. Maternal separation impairs long term-potentiation in CA3-CA1 synapses in adolescent female rats. *Behavioural brain research*. 2019;376:112239.
- [20] Shin S, Han S, Woo R-S, Jang S, Min S. Adolescent mice show anxiety-and aggressive-like behavior and the reduction of long-term potentiation in mossy fiber-CA3 synapses after neonatal maternal separation. *Neuroscience*. 2016;316:221-31.
- [21] Cao X, Huang S, Cao J, Chen T, Zhu P, Zhu R, et al. The timing of maternal separation affects Morris water maze performance and long-term potentiation in male rats. *Developmental psychobiology*. 2014;56(5):1102-9.
- [22] Gruss M, Braun K, Frey JU, Korz V. Maternal separation during a specific postnatal time window prevents reinforcement of hippocampal long-term potentiation in adolescent rats. *Neuroscience*. 2008;152(1):1-7.
- [23] Chocyk A, Bobula B, Dudys D, Przyborowska A, Majcher-Maślanka I, Hess G, et al. Early-life stress affects the structural and functional plasticity of the medial prefrontal cortex in adolescent rats. *European Journal of Neuroscience*. 2013;38(1):2089-107.
- [24] Joushi S, Esmaeilpour Kh, Masoumi-Ardakani Y, Esmaeili-Mahani S, Sheibani V, Intranasal oxytocin administration facilitates the induction of long-term potentiation and promotes cognitive performance of maternally separated rats. *Psychoneuroendocrinology* 2021; 123.
- [25] Joushi S, Esmaeilpour Kh, Masoumi-Ardakani Y, Esmaeili-Mahani S, Sheibani V, Effects of short environmental enrichment on early-life adversity induced cognitive alternations in adolescent rats. *Journal of neuroscience research*, 2021.
- [26] Xiong G-J, Yang Y, Wang L-P, Xu L, Mao R-R. Maternal separation exaggerates spontaneous recovery of extinguished contextual fear in adult female rats. *Behavioural brain research*. 2014;269:75-80.

- [27] Herpfer I, Hezel H, Reichardt W, Clark K, Geiger J, Gross CM, et al. Early life stress differentially modulates distinct forms of brain plasticity in young and adult mice. *PLoS One*. 2012;7(10):e46004.
- [28] Sousa VC, Vital J, Costenla AR, Batalha VL, Sebastião AM, Ribeiro JA, et al. Maternal separation impairs long term-potential in CA1-CA3 synapses and hippocampal-dependent memory in old rats. *Neurobiology of aging*. 2014;35(7):1680-5.
- [29] Guo L, Liang X, Liang Z, Liu X, He J, Zheng Y, et al. Electroacupuncture ameliorates cognitive deficit and improves hippocampal synaptic plasticity in adult rat with neonatal maternal separation. *Evidence-Based Complementary and Alternative Medicine*. 2018;2018.
- [30] Monroy E, Hernández-Torres E, Flores G. Maternal separation disrupts dendritic morphology of neurons in prefrontal cortex, hippocampus, and nucleus accumbens in male rat offspring. *Journal of chemical neuroanatomy*. 2010;40(2):93-101.
- [31] Bock J, Gruss M, Becker S, Braun K. Experience-induced changes of dendritic spine densities in the prefrontal and sensory cortex: correlation with developmental time windows. *Cerebral Cortex*. 2004;15(6):802-8.
- [32] Yang S, Li J, Han L, Zhu G. Early maternal separation promotes apoptosis in dentate gyrus and alters neurological behaviors in adolescent rats. *Int J Clin Exp Pathol*. 2018;10:10812-20.
- [33] Roceri M, Hendriks W, Racagni G, Ellenbroek BA, Riva MA. Early maternal deprivation reduces the expression of BDNF and NMDA receptor subunits in rat hippocampus. *Molecular Psychiatry*. 2002;7:609.
- [34] Garner B, Wood SJ, Pantelis C, van den Buuse M. Early maternal deprivation reduces prepulse inhibition and impairs spatial learning ability in adulthood: No further effect of post-pubertal chronic corticosterone treatment. *Behavioural brain research*. 2007;176(2):323-32.