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اثرات محیط غنی‌شده و اکسی‌توسین بر عملکرد شناختی در دوره نوجوانی موش‌های صحرایی نر جداشده از مادر

توسط: **سارا جوشی**

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Abbreviations	
ELA	Early life adversity
MS	Maternal separation
EE	Enriched environment
OT	Oxytocin
PND	Post natal day
LTP	Long term Potentiation
LTD	Long term Depression
RGT	Rat gambling task
PCT	Prosocial choice task
BDNF	Brain derived neurotrophic factor
MWM	Morris water maze
fEPSP	Field excitatory post-synaptic potential
PS	Population spike
PBS	Primed burst stimulation
aCSF	Artificial cerebrospinal fluid
BR	Both reward
OR	Own reward
SB	Social bias
HPA	Hypothalamus-pituitary-adrenal
HFS	High frequency stimulation
MAPK	Mitogen-activated protein kinase
CaMKII	Calcium-calmodulin dependent protein kinase II
NMDA	N-methyl-D-aspartate
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CREB	cAMP response element-binding protein
CTRL	Control group
ERK	Extracellular signal-regulated kinase
mTOR	Mammalian target of rapamycin

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چکیده

مقدمه و اهداف: تجارب اولیه زندگی شامل رفتار و مراقبت والدین، می‌توانند عملکردهای شناختی و رفتاری را در مراحل بعدی زندگی شکل دهند. نتایج مطالعات پیشین حاکی از آن است که جدایی از مادر (Maternal separation;MS) در اوایل زندگی استعداد ابتلا به بیماری‌های مرتبط با استرس را افزایش می‌دهد و ممکن است منجر به تغییر در عملکرد شناختی از جمله یادگیری و حافظه شود که این تغییرات تا بزرگسالی ادامه می‌یابند. یکی از فاکتورهای محافظت‌کننده و تعدیل‌کننده استرس، محیط غنی‌شده است که ترکیبی پیچیده از محرکات اجتماعی، فعالیت ذهنی و فیزیکی است. محیط غنی شده فرصت‌های بهتری را برای برهم‌کنش متقابل و کاوش کردن در محیط فراهم می‌کند. از طرف دیگر، مطالعات نشان داده‌اند که اکسی‌توسین از اختلالات یادگیری و نقص رفتار اجتماعی در بزرگسالی جلوگیری کرده و باعث کاهش اثرات استرس بر پلاستیسیتی و حافظه فضایی در هیپوکمپ موش‌های صحرایی می‌شود و هم‌چنین باعث کاهش اختلال در تقویت سیناپسی طولانی‌مدت (LTP[1]) می‌گردد. هدف از این مطالعه، بررسی اثرات محیط غنی‌شده و اکسی-توسین به‌صورت جداگانه و توام با یکدیگر بر عملکردهای شناختی، القای LTP و سطح بیان پروتئین BDNF[2] در موش‌های صحرایی نری است که در دوره نوزادی جدایی از مادر را تجربه کرده‌اند.

روش تحقیق: حیوانات در ده گروه مورد مطالعه قرارگرفتند. در گروه MS، نوزادان موش‌های صحرایی از روز ۱ تا ۲۱ پس از تولد روزانه به مدت ۱۸۰ دقیقه جدایی از مادر را تجربه کردند. سپس از PND[3] ۲۲-۳۴ (روز پس از تولد) در محیط غنی‌شده قرارگرفتند و/یا اکسی‌توسین (۲ µg/µl) را به‌صورت داخل بینی دریافت کردند و در PND ۳۵ (دوره نوجوانی) مورد سنجش بررسی‌های شناختی، الکتروفیزولوژی و مولکولی قرارگرفتند.

یافته‌ها: در حیوانات MS، کورتیکوسترون پلاسما و رفتار شبه اضطرابی افزایش یافت و فعالیت حرکتی کاهش یافت. هم‌چنین یادگیری و حافظه، رفتار اجتماعی و تصمیم‌گیری موش‌های MS دچار نقص شد. به‌علاوه، القای LTP در این موش‌ها دچار نقص شد و میزان BDNF هیپوکمپ کاهش یافت. محیط غنی‌شده و اکسی-

[1] Long term potentiation

[2] Brain-derived neurotrphic factor

[3] Post natal day

توسین رفتار شبه اضطرابی را کاهش داده و نقص‌های شناختی ناشی از MS را بهبود بخشیدند. هم‌چنین، این دو تیمار بر تخریب LTP ناشی از MS در ناحیه CA1 هیپوکمپ غلبه کردند.

نتیجه‌گیری: نتایج به‌دست‌آمده نشان داد که محیط غنی‌شده و اکسی‌توسین می‌توانند بهبوددهنده نقص‌های شناختی، پلاستیسیته سیناپسی و مولکولی ناشی از MS باشند.

کلمات کلیدی: جدایی از مادر، محیط غنی‌شده، اکسی‌توسین، شناخت، LTP، BDNF

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Abstract

Background and Objectives: Early-life experiences including parental care and behavior may affect cognitive and behavioral performnces later in life. Studies suggest that early-life maternal sepration (MS) enhances susceptibility to stress-related disorders and could induce some changes in cognitive functions such as deficits of learning and memory that may continiue through adulthood. One of the protective and stress-modulating factors is enriched environment (EE), that's a combination of physical, mental and social stimuli. EE provides more opportunities to explore and interact with the environment. Moreover, studies have been shown that oxytocin (OT) prevents learning and social behavior imparments at adulthood and reduces stress effects on plasticity and spatial memory in the rat hippocampus. on the other hand, OT decreases long-term potentiation (LTP) impairments. The aim of this study is to evaluate EE and OT effects, separately and in combination, on cognitive performance, LTP induction and BDNF expression levels in maternally separated male rats.

Methods: Ten groups were evaluated during this experiments. In MS group, rat pups were separated from their dam for 180 min/day from post natal day (PND) 1-21. From PND 22-34 rats experienced EE and/or received intranasal OT (2 µg/µl). On PND 35, rats were evaluated for cognitive, electrophysiological and molecular assessments.

Results: MS induced higher plasma corticosterone levels and more anxiety-like behavior and decreased locomotor activity. Impairments of learning, memory, social behavior and decision making were also observed as a result of MS. Moreover, LTP induction was impaired and hippocampal BDNF levels decreased due to MS. EE and OT could reduce anxiety-like behavior and improved MS-induced cognitive impairments. Moreover, these factors overcame MS-induced LTP impairments in CA1 area of hippocampus.

Conclusion: Obtained results showed that EE and OT could improve MS-induced impairments of cognitive performance, synaptic plasticity and molecular changes.

Keywords: Maternal Separation; Enriched Environment; Oxytocin; Cognition; LTP; BDNF

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In Partial Fulfillment of the Requirements for the Degree (PhD)

Title:

Effects of Enriched Environment and Oxytocin on Cognitive Performance During Adolescence in Maternally Separated Male Rats

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