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Research Article

Effects of Environmental Enrichment Paradigm on Learning and Memory Evaluations Depending on the Attempted Time in Life Span

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Abstract

Environmental enrichment (EE) has become a potential tool to impede the deficiency of cognition including learning and memory capacity in behavioral and psychiatric disorders. Tremendous of studies reported the magnificent profiles both in the animal model and preclinical treatments. The assessment of time aspects involved in the EE paradigm emerged as one of the crucial roles in the progress of improving cognition. The present mini-review elucidate the diverse effects depend on the time axis, aiming to shed light on the precise time-conscious selection when considering EE employment.

Keywords: Environmental Enrichment, Cognition, Learning and Memory, Time Axis.

Abbreviations: EE: Environmental Enrichment, CS: Compulsive Stress, PE: Physical Enrichment, AnPE: Anaerobic Physical Exercise, SE: Social Enrichment, MWM: Morris Water Maze, ORM: Object Recognition Memory, ELE: Early-Life Exposure, LLE: Late-Life Exposure, MS: Maternal Separation, CNP: C-type Natriuretic Peptide, STE: Short-Term Exposure, LTE: Long-Term Exposure, EZM: Elevated Zero Mazes, OCD: Obsessive-Compulsive Disorder (OCD).

Introduction

Species evolution starts at the point when creatures existed via the link between the capacity of learning and memory and surrounding. The better the capacity performs, the higher the species ranks. Sorts of literature had established the machinery of how the creature benefit from the ability of learning and memory, by which survived from the circumstance. The habituation and modification according to the external changes turned to be crucial traits which would be inherited to the progeny, through the regulation of both genetically and epigenetically. Although the genetic alteration requires astronomical decades evolution, which resulted from the numerous epigenetic modifications. Herein, cascade activities executed intracerebral connect the external environmental stimulus and molecular mediation, typically such as learning and memory.

Learning and memory processes depend on electrical and chemical signaling within the neural networks in the brain. This includes chemical signaling undertaken by amino acids, biogenic monoamines, acetylcholine, gasotransmitters, and peptides, as well as the neuropeptides and it's more than 20 distinct gene families [1]. Rodent models had convinced that learning and memory contribute to the molecular alteration intracerebral, thus, eliciting the neurogenesis or neuronal degradation. The

external environmental stimuli, no matter positive (Environmental Enrichment; EE) or negative (Compulsive Stress; CS) trigger this program by the neural plasticity, including synaptic plasticity or dendritic ramification.

The environmental enrichment (EE) stands for one of the positive mild stress, consists of physical abundance, initiative social connection, and voluntary exercise, classically defined as "EE paradigm" which provides animals with enriched, multiple lifestyles causing brain changes at the functional, anatomical, and molecular level, further influents the capacity of learning and memory, and cognition as well [2]. Multidimensional assays testing on spatial learning and memory such as Morris Water Maze (MWM), Object Recognition Memory (ORM), fear conditioning, and social novelty test had convinced the approvals of EE beneficial effects on neurogenesis, neurotrophic factors, synaptic plasticity, and neurotransmitter systems [3], specifically in aged mammals models in EE 60 years developmental history since it's established [4]. There is no doubt EE conditions improve learning and memory thorough synaptogenesis, increasing dendritic arborization, and spine density manners in all age-range rats models, no matter in prepuberty, adults, or aged animals [5], same do in various forms such as social enrichment, physical exercise, or cognitive enrichment. In terms of the consequences of EE on learning and memory, some were transient, some were lifelong.

Extending effects of EE on learning and memory were determined by the diversity of EE strategies in a time-conscious manner. Exposure into EE for a long time, or a short time, or with early-life onset, or with late-life onset, resulted in distinguish consequence and revealed the distinct mechanism. Here, we mini-reviewed the different EE patterns depend on the time-axis to delineate the specified machinery underlying the alteration of learning and memory on the basis of specified EE exposure in rats model.

Catalogs of EE paradigms

EE has become a strategic paradigm in brain plasticity related to brain disease treatment options. However, different patterns specialized in distinct strategies in various laboratories. Canonical EE protocols utilize the common procedure that rats rearing in a large chamber with or without provides ad libitum. Multifactorial EE embraces Social Enrichment (SE), Cognitive Enrichment (CE), and Physical Enrichment (PE), which stands for social contact, novelty, and exercise application respectively [6]. It is not easy to set 3 factors apart precisely to exert EE procedure in rats' models, while the majority of researches utilized factors combination. The isolative neuroprotection was demonstrated by three interventions - Cognitive Enrichment (CE), Anaerobic Physical Exercise (AnPE), and Social Enrichment (SE) that CE and AnPE have better neuroprotective effects than SE in memory deficits induced by oxidative stress via Aβ intrahippocampal infusion [7]. Nevertheless, a study dissociated the effects of SE, presenting higher cognitive benefits rather than other forms of enrichments, consistent with the finding of divorced effects among the different forms of enrichments [8]. Integrating of CE and PE strategy in transgenic Gfap-tk mice clearly demonstrated the improvements in the overall number of progenitor cells and neurogenesis for learning and memory processes as well [9]. Exclusive effects upon CE and SE recapitulated that CE promoted miR-123, miR-132, and neurogenesis in the dentate gyri of the hippocampus, while SE preferred the promotion in increased prosocial 50-kHz ultrasonic vocalizations emission rates and minor brain plasticity. Furthermore, keypoint is that social deficits following CE were reversed by SE indicated CE and SE displayed the opposite performance in social behavior [10]. Besides, on top of mammals' models, Abreu and his colleagues recapitulated the complex pattern of EE combined exercise and visuospatial enrichment contributed to the learning and memory enhancement in increasing cell proliferation in the telencephalon via the gold fish (Carassius auratus), a behavioral study fish model [11].

In summary, 3 categories of EE paradigm are the potential options for the study on the learning and memory machinery based on the coherent determinants featuring each element:

1. Social Enrichment, subjects are housed in larger groups of animals compared with standard cages,

2. Cognitive enrichment, which includes exposure to novel stimulation and experiential learning (toys and tunnels).

3. Physical enrichment, consisting of voluntary exercise (access to running wheels) [12].

Another measure of the category is based on the time-axis, depend on the initiation and duration of EE employment respectively. Although the influences of EE are profound and perpetual, which stage of lifeline initiating the EE and how long it lasts lead to different outcomes in learning and memory studies. Apparently, long-term and early-life EE implements prone to more significant performance compare to those in short-term and late-life in rats model. The effects and machinery are more likely sophisticated if counted in the forms of EE. The complex of EE patterns was induced when considering the timeline aspects, for instance, PE and CE elevated the cognition rather than CE alone in aged rats (over 14 months) but showed the detriments in spatial learning and memory in young age model (less than 4 months) [13]. The consensus is that the time-axis EE pattern in various related studies to demonstrate the effects specialized into distinct EE paradigm, therefore provide the auxiliary thoughts for the preclinical treatment along with pharmacotherapy.

Effects of learning and memory depend on the discrepancy of EE onset time

A typical study reviewed the equivalent age between laboratory rats and humans being determined by the precise period lifespan [14]. The diversity of the relationship between rats and human depend on the developing-hood they existed in terms of some formulas calculated according to the finding. The pan-equivalent lifelong is the very day of the rat resembles 34.8 human days signified the variations in anatomy, physiology, and developmental processes. Regarding this, approximately those onset time of EE exposure less than 9 months of age of rats were categorized into Early-Life Exposure (ELE; equal to 23-years old human), contrast, those rats onset more than 9 months were categorized into Late-Life Exposure (LLE) in the present review [14]. Given the different timeline owning discrepancy in EE effects in ELE and LLE respectively, the mechanism underlying learning and memory alteration was disparities.

Established evidence about very early life exposure in ELE environment initiated from postnatal day P8~21 as the pre-weaning period with lactation, alleviated the perpetual deficit of the learning process which resulted from protein malnutrition [15]. EE early in life recognized as a powerful neuroanatomical reorganization tool benefit the number and size of CA1 neurons during brain development. The most intriguing in this study was that they provided another ELE pattern at the age of P22~35 in a larger and multiform chamber compare to the former one while resulted in a similar outcome. Potential therapeutic function for the prevention of drug addiction of ELE (P21~50) was dug out by the voluntary consumption of morphine test conducted in the cohorts of the maternal separation (MS) and EE rats. ELE rats were found lower voluntary consumption of morphine compare to MS and standard [16].

Later onset exposure of ELE on postnatal day 23 lasted for 6 weeks, prepuberty of rats, aimed to validate the compensatory role of EE against a negative outcome in the MS model early in life, resulting from restored neuroendocrine and synaptophysin/BDNF expression [17]. A comparative study between young (8~9 months) and aged (22~23 months) male rats elicited the putative upregulation in neuroprotection, neuroplasticity and learning and memory via extending to C-type natriuretic peptide (CNP) bioactive valuation. CNP, a proposed neuroendocrine regulator, recognized as an EE effective marker and was determined by NTproCNP, the amino-terminal fragment of proCNP, whereas the ratio NTproCNP: CNP is a biomarker of CNP's local degradation rate. 2-weeks lasting EE stimuli elicited increased CNP in young rats rather than old counterparts but eliminated at 28 days. Other than NTproCNP, NTproCNP: CNP ratio showed downregulation in young rats instead of old rats [18].

Different brain regional selection – orbitofrontal cortex for specific memory - system consolidation research conducted at a 14-month model to test EE effects on aged animals. Immediate early gene family c-fos and epigenetic marker, histone H3 acetylation, declined in the aged model were ameliorated by long-term EE paradigm [19], as well as ascending memory assessment in the social transmission of food preference test. The hippocampal functional reinforcement by LLE was consistent with ascending assessments upon metabotropic glutamate receptor-dependent long term potentiation (mGluR-LTP), phospho-p70S6 kinase in old rats aged 23-24 months [20].

The older the EE employment animal was, the fewer effects it supposed to be. EE successfully maintained the accurate recent and remote spatial memory in the 17~24-month-old female rats while displayed less functional alleviation at the age of 24-month [21]. LLE had the reluctant upgrade mediation in aged rats compared to those in young or adult rats. This retarded EE-associated elevating carve may be due to the belated epigenetic modification such as H3 acetylation on the bdnf gene at the promoter I, as well as proximal nuclear factor κ B (NF-κB) site [22]. The similar "reserve" - like advantage EE elicited was shown in another research which indicated that late EE mitigated the spatial memory deficit in those previously unexposed to EE instead of those exposed to EE before [23].

Taken together, the mechanism underlying the EE effects of learning and memory depend on the onset at different stages of the lifecycle probably distributed to the alterations of BDNF [16,22], neuroanatomical reorganization [17], c-fos and H3-Ac elevation [19], mGluR-LTP [20], et cetera. ELE and LLE share the common benefits of hippocampus-dependent learning and memory while leading to a significant phenomenon: LLE owns the late-blooming and flat carve in cognitive enhancement related to ELE [18,21].

Effects of learning and memory depend on the discrepancy of EE exposure duration

According to formulae [14], calculating the age equivalent between rat and human, approximately 5-year training for patients in clinical equal to 8-week long EE application in rats' model. Regarding this, maintaining in EE less than 8 weeks was identified as Short-Term Exposure (STE), correspondingly, those over 8 weeks were identified as Long-Term Exposure (LTE). Each paradigm featured the distinguished characters and properties in effects on learning and memory in rats model.

The differential outcome derived from STE and LTE respectively. Efforts had dedicated to STE for 3-week EE exposure, resulted in enhances NMDAR-dependent LTP, increases the expression of p-CREB and VEGF, but not BDNF, while, caused weight loss and did not affect the immunoreactivity of several synaptic or cellular

markers [24]. On the opposite, the 12-month implementation of LTE markedly boosted hypertrophy and ramification in microglial morphology, reduced microglial and neuroinflammatory markers, IBA-1, improving learning, and memory through anti-inflammatory way [25]. Nevertheless, apart from the rats model, a mice study preserved in the LTE for 7-8 weeks reinforced the theory that EE significantly enlarges the microglial density and branching in DG of the hippocampus, as well as prevented the multiple inflammatory genes both in vivo and in vitro [26]. Furthermore, in behavioral test battery, LTE reduced locomotion in the open-field test, whereas STE reduced the mean body weight and showed anxiolytic effects in the elevated zero mazes (EZM) [27]. There is no doubt that STE is sufficient to provided resilience against maladaptive effects of stress, typically in the current [28]. In comparison, LTE was easier to elicit epigenetic modification in histone acetylation owing to long-term EE intervention [22]. The novelty of EE properties was readily reserved in STE while rendering into chronic, mild stress if it maintained for a long time, resulting in LTE present fewer surviving neurons than STE in Kainate-lesioned rats [29].

Both STE and LTE contributed the promotion of learning and memory capacity, specifically in hippocampus way, While Lajud and collaborators suspected the machinery underlying the mitigation of cognition detriment from the TBI model, clarified that even both early + continuous EE and delayed + abbreviate EE exhibited the similar, comparable increases in cognitive recovery, while only early + continuous EE, not delayed + abbreviate EE, showed the ascriptions on hippocampal neurogenesis [30]. This version of distinguishment between LTE and STE clarified the crucial role of continuous, maintenance of EE employment.

Discussion and Clinical perspective

EE had become one of the clinical strategies for a long time in diverse ways. The majority of employment of EE confers to the resilience of aged patients or those disabilities. The options of EE in pre-clinical administration various in which forms chosen, LTE or STE, ELE or LLE, whether combined with pharmacological treatments or not, et.al. it is elusive to ascertain which one is better, depending on the protocols and pursuing in the ongoing research. The efforts of EE possibilities of extending into preclinical lighted the prospects both in animal trials or human real life.

EE has been putatively introduced into the preclinical treatment in terms of its neurogenesis, synaptogenesis, and neuronal migration functions posterior to manipulated stroke employment [31]. Another instance upon inducing EE as a clinical treatment to reconcile obsessive-compulsive disorder (OCD) revealed the EE potential perspective on the attenuation of obsessive-compulsive behavior [32]. Emerging studies engaged in the EE complex to facilitate the reinforcement of clinical strategies. EE combining with pharmacological treatments such as Spirulina platensis illustrated the elevating effects in BDNF alternation and cognitive performance in chronic stress adolescent rats model [33]. However, it is still not easy to draw a conclusion that the EE complex performs better than EE alone. Both EE and aripiprazole, possessing partial D2 and 5-HT1A receptor agonist activities, dramatically improved the recovery of learning and memory in the traumatic brain injured (TBI) rats model respectively, while did not yield additional benefits in combined trials [13]. As mentioned above, other than OE, SE became an auxiliary preclinical application as a potential treatment for neuropsychiatric disorders characterized by social deficits, for instance, autistic spectrum disorder [10].

Considering the time factors which might affect the outcome of EE in learning and memory improvements, the time-axis or the exposure duration of EE play role in the mechanism underlying the cognitive alteration. Generally, the effects of STE last in a short time compare to LTE since lack of sufficient epigenetic modification which LTE owing. On the other hand, the enhancement of ELE might easier to be elicited and affect more profound than LLE since its onset in the brain developing period. The discrepancies of EE implements remained, phenomenally and diversely.

The disparities of multidimensional forms of EE even in one single pattern had been considered in the preclinical strategies. A study was of distinguishing effects between 3-hr periods of EE vs. a single 6-hr session, replicated that 6-hr of EE daily is sufficient to reverse the deficits from TBI, against the previous hypothesis that neurorehabilitation in two 3-hr periods of EE would be better than the other one [34]. The putative suggestion extended to the clinic that EE treatment for the patients might consider the total comparable volumes ignoring the way how EE time was accrued. Another similar study concreted the conclusion, adding the extra proof that rehabilitative effects were augmented combined with galantamine [35]. Additionally, EE efficiency can't be calculated over time, as mentioned [23], which performs the enhancement of learning and memory in those null rats other than those experienced EE previously. Given the considering of dominants of ELE and LTE, a recent report combined ELE and LTE to demonstrate EE, as a neuroprotective tool, has been turned into a pan-effective manner in development modulates energy metabolism and reduction of oxidant stress via implementing ELE perinatal lasting for 6 months [36]. Numerous evidence showed that the onset time and duration of environmental interventions are critical in terms of their ability to modify gene expressions, such as selectively enhance 5-HT gene expression and the functional consequences on behavioral pharmacology [37]. An intriguing real-world trial underlined the hypothesis that STE in humans even in the 7-month intervening (equal to 1-week STE in rats according to the formula: rats days 34.8 = 1 day in human) ameliorated the symptoms of autistic spectrum disorder (ASD) [38].

The estimation of time aspects in the EE paradigm is still ongoing. The profound effects derived from epigenetic modification emerged recently, revealed the intranuclear machinery upon time imprinting along with environmental stimulations. Further efforts would be dedicated to the links of molecular modulation to the therapeutic effects of environmental stimulation beyond neurodegenerative disease.

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Conflict of Interest

None.

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