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REVIEW PAPER

Can Environmental Enrichment Modulate Epigenetic Processes in the Central Nervous System Under Adverse Environmental Conditions? A Systematic Review

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Abstract

The aim of this paper is to summarize the available evidence in the literature regarding the effects generated by exposure to an enriched environment (EE) on the modulation of epigenetic processes in the central nervous system under adverse environmental conditions. Searches were conducted in three databases: PubMed/Medline (1053 articles), Scopus (121 articles), and Embase (52 articles), which were subjected to eligibility criteria. Of the 1226 articles found, 173 duplicates were removed. After evaluating titles/abstracts, 904 studies were excluded, resulting in 49 articles, of which 14 were included in this systematic review. EE was performed using different inanimate objects. Adverse environmental conditions included CUMS, sepsis, nicotine exposure, PCP exposure, early stress, WAS, high fructose intake, TBI, and sevoflurane exposure. Regarding microRNA expression, after exposure to EE, an increase in the expression of miR-221 and miR-483 was observed in the prefrontal cortex, and a reduction in the expression of miR-92a-3p and miR-134 in the hippocampus. Regarding histone modifications, in the hippocampus, there was a reduction of HAT, HDAC/HDAC4, H3 (acetyl K14), H4 (acetyl K15), H3K4me3, K3k27me3, and HDAC2/3/5. In the cortex, there was a reduction of HDAC2, and in the prefrontal cortex, there

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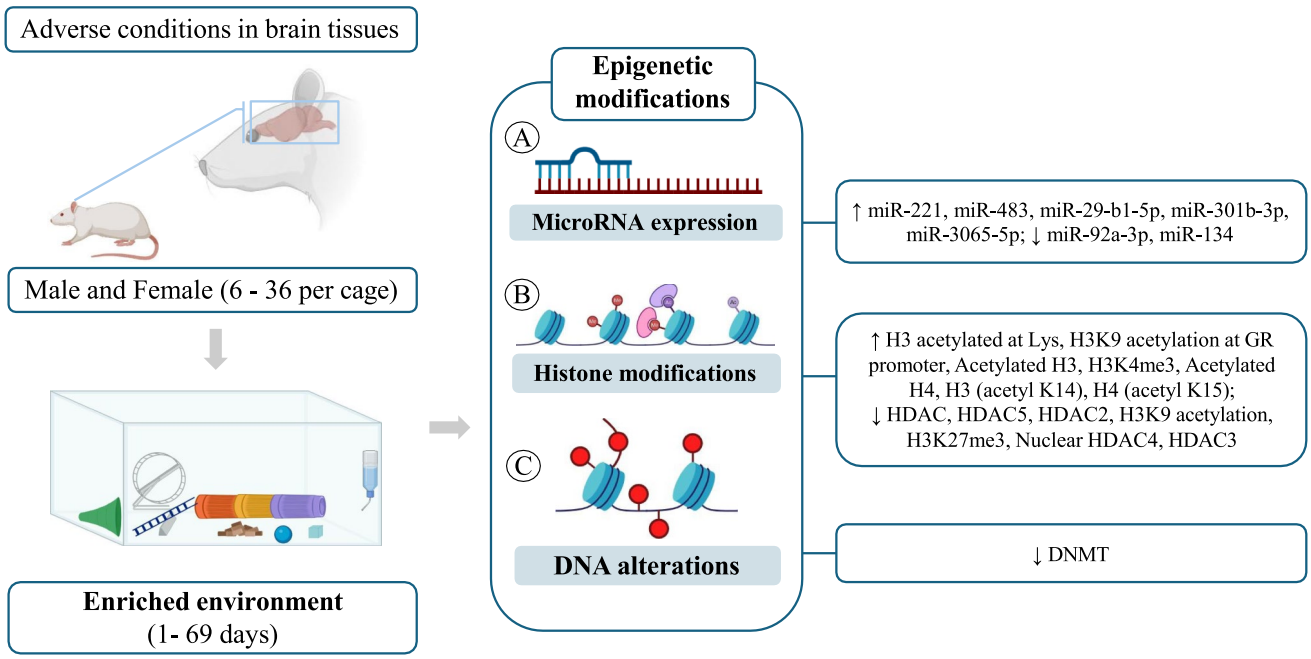
was an increase in acetylated H3. Regarding DNA modifications, there was a reduction of DNMT in the hippocampus. This systematic review concludes that the benefits of EE on the brain and behavior of animals are directly related to different epigenetic mechanisms, reflecting in cell growth and neuroplasticity. EE may be a non-pharmacological and easy-to-apply alternative to prevent symptoms in disorders affecting brain tissue.

Graphical abstract



Keywords Enriched environment · Epigenetics · Histones · MicroRNA · Nervous system

Introduction

Epigenetics was initially described by Waddington in the 1940s, specifically using the term "epigenetic landscape" to refer to the events that lead to the unfolding of the genetic program, which influences the resulting phenotype through the interaction between genes and the environment (Wang et al. 2011; Feinberg and Levchenko 2023).The mechanisms involved in epigenetic regulation are related to gene expression but do not involve changes to the DNA sequence; these molecular processes include DNA methylation, histone modifications, and the expression of non-coding RNAs (Fitz-James and Cavalli 2022).

DNA methylation can be succinctly described as the covalent addition of a methyl group to one of the nucleotides in the DNA molecule, most commonly associated with the methylation of the CpG dinucleotide (cytosine followed by guanine). This modification plays a crucial role in transcriptional regulation and phenotypic inheritance, as it can prevent the binding of transcription factors while recruiting proteins that compact chromatin. Consequently, this makes the DNA inaccessible for transcriptional processes (Li and Tollefsbol 2021). Histones make up the nucleosome, the functional unit of chromatin, and can either increase or decrease its compaction, thereby playing a role in gene expression regulation. This process is mediated by numerous modifications occurring on the N-terminal tails of these histone proteins (such as acetylation, ubiquitination, and phosphorylation); acetylation is catalyzed by the enzyme acetyltransferase (HAT), while deacetylation occurs through the enzyme histone deacetylase (HDAC). These enzymes are well-documented in the literature and are important mechanisms of epigenetic inheritance (Fitz-James and Cavalli 2022; Yu et al. 2020).

The expression of non-coding RNAs is another fundamental process for modifying the epigenetic state, capable of regulating gene transcription in various ways; one such example is the synthesis of microRNAs (miRNAs), which are small RNAs (19–22 nucleotides in length) formed in the cell nucleus and transported to the cytoplasm. These miRNAs are responsible for blocking messenger RNA (mRNA) translation by binding to target genes, thereby preventing the expression of the corresponding protein (gene silencing) or inducing the degradation of the mRNA (McKibben and

Dwivedi 2021; Carthew and Sontheimer 2009; Yan and Bu 2021). All these mechanisms characterize the expression of the phenotypic state and are involved in various biological processes that affect aspects of health and disease, having a profound relationship with the environment.

Currently, environmental enrichment can be considered a fundamental aspect of animal housing and management; it involves modifications that provide physical, social, and cognitive stimuli, holding importance equal to nutritional precautions. This enrichment allows animals to engage in species-specific activities, positively influencing their quality of life, both in healthy individuals and those with certain conditions, such as neurological diseases (Baumans 2005; Gomez et al. 2015).

There is a wide variety of disorders that impact the nervous system, ranging from neurodevelopmental disorders to neurodegenerative diseases that predominantly affect the elderly. Additionally, trauma and disorders secondary to other pathological conditions, such as infectious diseases that result in damage to nervous tissue, can also be mentioned (Global, regional, and national burden of disorders affecting the nervous system 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021 2024). These unfavorable conditions related to the nervous system are strongly influenced by the environment and gene regulation mediated by epigenetic factors (Nikolac Perkovic 2021; Ghosh and Saadat 2023).

Exposure to an enriched environment is associated with various benefits for the nervous system; there is evidence that an enriched environment can stimulate myelination and repair of nervous tissue by increasing the secretion of molecules that regulate the development and myelination of nerve cells. This has significant importance in various neuropathological conditions (Gao et al. 2022). Studies with animals have also demonstrated benefits in social behavior, increased synaptic density in the hippocampus, elevated expression of dopamine receptor D2, promotion of neuronal recovery, changes in extracellular concentrations of glutamate and GABA, and enhanced learning flexibility. All these effects are mediated by sensory, cognitive, and social stimuli generated by an enriched environment, which trigger adaptive responses in the nervous system that impact various neurological contexts (Han et al. 2022). The benefits of exposure to an enriched environment also include the reversal of symptoms in pre-established pathological conditions, such as sepsis, by preventing cognitive losses associated with neurodegeneration. This leads to improved brain function, as evidenced by a reduction in long-term memory impairment (Córneo et al. 2022).

Given the significant influence of the environment on modifying the epigenetic profile, the stimuli provided by environmental enrichment can alter the phenotypic state resulting from changes in gene expression. However, the underlying mechanisms are not yet fully elucidated, particularly in adverse conditions such as pathologies and injuries. One major issue is the lack of standardized protocols. Clarifying the relationship between environment and epigenetic factors could be crucial for developing new therapeutic strategies based on enriched environments.

The present study aims to conduct a systematic review to understand the impacts of environmental enrichment on key epigenetic changes in the nervous system, analyzing DNA methylation, histone modifications, and non-coding RNA expression (miRNAs) under adverse conditions.

Methods

This systematic review was conducted following the PRISMA guideline (Page et al. 2020).

Eligibility Criteria

The selection of studies followed the eligibility criteria drawn up in accordance with PECOS (Population: rodents; Exposure: adverse environmental conditions; Control: standardized environment associated with adverse conditions; Outcomes: epigenetic processes [expression of microRNAs, modifications related to histones and DNA]; Studies Design: animal studies). No limitations on publication time and language were established in the selection of studies. Original studies were selected, while dissertations or theses, study protocols, review articles, gray literature, editorials, summaries, and articles that did not evaluate rodents, brain tissues, adverse environmental conditions, or epigenetic processes, or that did not present a control group exposed to the standardized environment associated with adverse environmental conditions, were excluded.

Information Sources and Search Strategy

Three electronic databases were used to search for articles (PubMed, Scopus, and Embase). The research was carried out in June 2024. The following search equation was used: ((Enriched environment) OR (Environmental enrichment)) AND (((((((((Epigenetic Processes) OR (Epigenetic Process)) OR (Histones)) OR (Histone)) OR (MicroRNAs)) OR (Micro RNA)) OR (MicroRNA)) OR (miRNA)) OR (miRNAs)). Adaptations were made for electronic databases. No filters were used to search for articles. The search for studies was carried out in pairs, with discrepancies resolved by a third evaluator.

Selection Process

Study selection was carried out with the help of Endnote X20 software (Clarivate Analytics, Philadelphia, USA). Duplicates were removed, and then studies were screened by reading titles and abstracts. Subsequently, the full texts were evaluated. This process was carried out by two researchers, and discrepancies were resolved by a third evaluator.

Data Collection Process

Data collection took place independently by two evaluators (MSSF and GCJS). Discrepancies were resolved by a third evaluator.

Data Items (outcomes)

Data were extracted about the study (author and year), animal characteristics (species, sex, age), and information on the number of animals per cage; environmental enrichment protocol, housing dimensions (length, width, and depth or height, in centimeters or meters), and exposure time of the environmental enrichment in weeks were collected. Finally, we also added information about the brain tissue used, type of adverse environmental condition, and environmental modifications.

Methodological Quality Assessment

The SYRCLE's strategy was used to assess the methodological quality of the animal studies. The tool consisted of ten questions that evaluate methodological criteria: Q1—Was the allocation sequence adequately generated and applied? Q2—Were the groups similar at baseline or were they adjusted for confounders in the analysis? Q3—Was the allocation to the different groups adequately concealed? Q4—Were the animals randomly housed during the experiment? Q5—Were the caregivers and/or investigators blinded from knowledge of which intervention each animal received during the experiment? Q6—Were animals selected at random for outcome assessment? Q7—Was the outcome assessor-blinded? Q8—Were incomplete outcome data adequately addressed? Q9—Are reports of the study free of selective outcome reporting? Q10—Was the study free of other problems that could result in a high risk of bias? Questions were answered with options of 'Yes,' 'No,' or 'Not clear.' When the answer was 'Yes,' a score was given; when the answer was 'No' or 'Not clear,' no score was given. The overall scores for each article were calculated on a scale of 0–10 points, with the quality of each study being classified as high (8–10), moderate (5–7), or low (< 5). The quality outcomes are described in Table 1.

Table 1 Methodological Quality Assessment

Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Córneo et al., 2022	Y	Y	Y	Y	N	Y	N	U	Y	U
Gomez et al., 2015	Y	Y	Y	Y	N	Y	N	U	Y	U
Ji et al., 2023	Y	Y	Y	Y	N	Y	N	U	Y	U
Koseki et al., 2011	Y	Y	Y	Y	N	Y	N	U	Y	U
Lin et al., 2020	Y	Y	Y	Y	N	Y	N	U	Y	U
Mckibben et al., 2021	Y	Y	Y	Y	N	Y	N	U	Y	U
Min et al., 2022	Y	Y	Y	Y	N	Y	N	U	Y	U
Orock et al., 2021	Y	Y	Y	Y	N	Y	N	U	Y	U
Seo et al., 2021	Y	Y	Y	Y	N	Y	N	U	Y	U
Shen et al., 2019	Y	Y	Y	Y	N	Y	N	U	Y	U
Wang et al. ,2016	Y	Y	Y	Y	N	Y	N	U	Y	U
Wu et al., 2016	Y	Y	Y	Y	N	Y	N	U	Y	U
Xin W et al., 2018	Y	Y	Y	Y	N	Y	N	U	Y	U
Yu et al., 2020	Y	Y	Y	Y	N	Y	N	U	Y	U

Q1. Was the allocation sequence adequately generated and applied? *Q2* Were the groups similar at baseline or were they adjusted for confounders in the analysis? *Q3* Was the allocation to the different groups adequately concealed during? *Q4* Were the animals randomly housed during the experiment? *Q5* Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment? *Q6* Were animals selected at random for outcome assessment? *Q7* Was the outcome assessor-blinded? *Q8* Were incomplete outcome data adequately addressed? *Q9* Are reports of the study free of selective outcome reporting? *Q10* Was the study apparently free of other problems that could result in high risk of bias? *Y* Yes; *N* No; *U* Unclear

Results

Methodological Quality Assessment

The quality of the included studies is shown in Table 1. All studies showed adequate and randomized allocation with randomly selected rodents. Furthermore, incomplete results were handled appropriately, free from selective results and bias. Because these are studies with adverse conditions and environmental enrichment, it is not possible to consider the investigation and analysis of the results blind. In general, all studies presented good quality criteria.

Search Results

In total, 1226 articles were found in the databases [PubMed/Medline ($n=1053$), Scopus ($n=121$), and Embase ($n=52$)]. Subsequently, 173 duplicates were removed, leaving 953 for screening. After screening, 904 articles were excluded, leaving 49 for analysis based on the eligibility criteria. Finally, 14 articles were included (Fig. 1).

Study Characteristics

The description of the included studies and environmental enrichment protocols is detailed in Table 2. The selected studies were published between the years 2011 and 2023, with the majority being published from 2020 onward ($n=9$, 64.2%). Among the species of animals used in the study were observed the species: Sprague Dawley ($n=4$) (Gomez et al. 2015; Wu et al. 2016; Shen et al. 2019; Ji and Zhao 2023), C57BL/6 ($n=4$) (McKibben and Dwivedi 2021; Lin et al. 2020; Seo et al. 2021; Min et al. 2022), Kunming ($n=2$) (Wang et al. 2016; Wang et al. 2018), Wistar ($n=1$) (Córneo et al. 2022), ICR ($n=1$) (Koseki

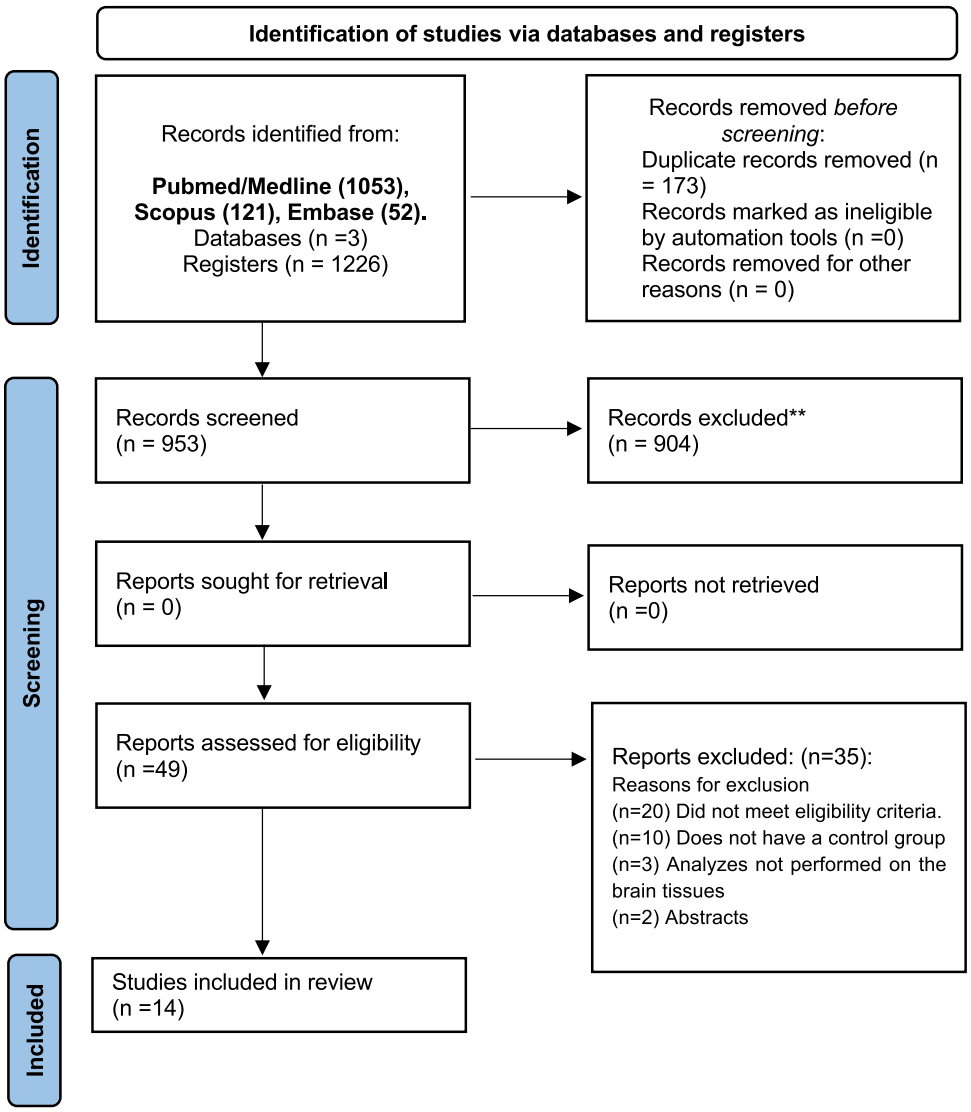


Fig. 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

Table 2 Sample characteristics and environmental enrichment protocol

Author, year	Species, age	Sex	*n per cage*	Environmental Enrichment Protocol and Housing dimensions		Exposure time to environmental enrichment
				Type of environmental enrichment and inanimate objects	(Length, Width, Height)	
Córneo et al., 2022	Wistar, 60 days old	M	10	Physical and Social Enrichment; Running wheels, toys, small house	80×45×22 cm	45 days
Gomez et al., 2015	Sprague Dawley, 21 days	M	10–15	Physical and Social Enrichment; Plastic objects	120×60×45 cm	–
Ji et al., 2023	Sprague Dawley, 6 wks old	M	10	Physical and Social Enrichment; Running wheels, plastic-colored toys, houses, tunnels, and stairs	100×80×80 cm	3 wks
Koseki et al., 2011	ICR mice, 3 wks old	M	8	Physical and Social Enrichment; Running wheels, toys, tunnels, and hiding places	50×70×20 cm	4 wks
Lin et al., 2020	C57BL/6 mice, 6–7 wks	M	6	Physical and Social Enrichment; Running wheels, wooden toys, tunnels, igloos, huts, and retreats	90×70×30 cm^3	6 days
Mckibben et al., 2021	Holtzman Rats, C56BL/6;	M/F	–	Physical and Social Enrichment; Toys, tubes, shreddable cotton, paper objects, and manzanita wood	–	69 days
Min et al., 2022	C57BL/6 mice, 8 wks	M	3–5	Physical and Social Enrichment; Running wheels, toys, tunnels, and shed	43.18×22.86×19.05 cm	3, 7, and 14 days
Orock et al., 2021	Fischer-344 mice, 5wks	F	8	Physical and Social Enrichment; Toys, ramps with ample bedding, tunnels, and food enrichment	78×52×100 cm	1–7 Days
Seo et al.2, 021	C57BL/6j mice; 8 wks	F	6–8	Physical and Social Enrichment; Running wheels, tunnels, small balls, and shaped blocks	26×42×18 cm^3	5 wks
Shen et al., 2019	Sprague Dawley, 10 wks	M	8	Physical and Social Enrichment; Running wheels, toys, tunnels, house, and differently shaped objects	100×80×80 cm	3 wks
Wang et al., 2016	Kunming mice, 8 wks	M	25	Physical and Social Enrichment; Running wheels and toys	60×33×28 cm	4 wks
Wu et al., 2016	Sprague Dawley, 7 wks	F	36	Physical and Social Enrichment; Plastic toys and nesting material	10.5×19×18 inch	4 wks

Table 2 (continued)

Author, year	Species, age	Sex	*n per cage*	Environmental Enrichment Protocol and Housing dimensions		Exposure time to environmental enrichment
				Type of environmental enrichment and inanimate objects	(Length, Width, Height)	
Xin W et al., 2018	Kunming mice, 6–8 wks	M	30	Physical and Social Enrichment; Running wheels and toys	60 × 36 × 28 cm	4 wks
Yu et al., 2020	Rats, 6 wks old	M	13	Physical and Social Enrichment; Running wheels, toys, tunnels, shelters, ladder trapeze, and balls	83 × 83 × 83 cm	2 wks

cm centimeters; *wks* weeks; *M* Male; *F* Female

et al. 2012), Fischer-344 ($n = 1$) (Orock et al. 2021), and Holtzman ($n = 1$) (McKibben and Dwivedi 2021). The animals used were aged between 21 days (Gomez et al. 2015) and 10 weeks (Shen et al. 2019). These rodents in their development period pass through the period of gestation and lactation (Gomez, et al. 2015) until the young age (Shen et al. 2019), and most of the protocols used only male animals ($n = 10$).

Environmental enrichment was performed using different inanimate objects, with the majority being toys ($n = 11$) (Yu et al. 2020; McKibben and Dwivedi 2021; Córneo et al. 2022; Wu et al. 2016; Ji and Zhao 2023; Lin et al. 2020; Min et al. 2022; Wang et al. 2016, 2018; Koseki et al. 2012; Orock et al. 2021), running wheels ($n = 10$) (Yu et al. 2020; Córneo et al. 2022; Shen et al. 2019; Ji and Zhao 2023; Lin et al. 2020; Min et al. 2022; Wang et al. 2016, 2018; Koseki et al. 2012; Orock et al. 2021), tunnels ($n = 8$) (Yu et al. 2020; Shen et al. 2019; Ji and Zhao 2023; Lin et al. 2020; Seo et al. 2021; Min et al. 2022; Koseki et al. 2012; Orock et al. 2021), houses ($n = 2$) (Córneo et al. 2022; Ji and Zhao 2023), and balls ($n = 2$) (Yu et al. 2020; Seo et al. 2021). Other identified objects were plastic objects, stars, hiding places, huts, retreats, tubes, shreddable cotton, paper objects, manzanita wood, shed, ramps, food, shaped blocks, nesting materials, shelters, ladders, and trapeze. Additionally, the size of the boxes used to accommodate the animals varied with heights ranging from 26 (Seo, et al. 2021) to 120 cm (Gomez, et al. 2015), widths from 22.86 (Min et al. 2022) to 83 cm (Yu et al. 2020), and lengths from 18 (Seo et al. 2021) to 100 cm (Orock et al. 2021). The duration of environmental enrichment varied among the protocols, lasting from 1 day (Orock et al. 2021) to 69 days (McKibben and Dwivedi 2021), with most studies using protocols that lasted between 3 and 4 weeks (Wu et al. 2016; Shen et al. 2019; Ji and Zhao 2023; Wang et al. 2016, 2018; Koseki et al. 2012). All included studies carried out an environmental enrichment protocol based mainly on physical and social stimuli according to the standardization defined by Hosey and collaborators (Hosey et al. 2013).

The description of the adverse exposure condition, evaluated brain tissue, and epigenetic changes is detailed in Table 3. Various exposure protocols were used: CUMS ($n = 3$) (Shen et al. 2019; Ji and Zhao 2023; Seo, et al. 2021), stroke ($n = 2$) (Lin et al. 2020; Wang et al. 2016), sepsis ($n = 1$) (Córneo et al. 2022), nicotine exposure ($n = 1$) (Gomez, et al. 2015), PCP exposure ($n = 1$) (Koseki et al. 2012), early life stress ($n = 1$) (McKibben and Dwivedi 2021), POCD ($n = 1$) (Min et al. 2022), WAS ($n = 1$) (Orock et al. 2021), high fructose intake ($n = 1$) (Wu et al. 2016), TBI ($n = 1$) (Wang et al. 2018), and sevoflurane exposure ($n = 1$) (Yu et al. 2020). The expression of epigenetic changes occurred in various brain tissues such as the hippocampus ($n = 8$) (Yu et al. 2020; Córneo et al. 2022; Wu et al. 2016; Shen et al. 2019; Ji and Zhao 2023; Seo, et al. 2021; Min et al. 2022; Wang et al. 2016), prefrontal cortex ($n = 3$) (Gomez, et al. 2015; Wang et al. 2018; Koseki et al. 2012), cortex ($n = 2$) (Lin et al. 2020; Min et al. 2022), amygdala ($n = 1$) (Orock et al. 2021), and forebrain ($n = 1$) (Wang et al. 2016).

Environmental Enrichment and Expression of Micrornas

Four studies evaluated the expression of microRNAs, with two in the hippocampus (miR-92a-3P, miR-134) (Shen et al. 2019; Ji and Zhao 2023), one in the prefrontal cortex (miR-221, miR-483) (Gomez, et al. 2015), and one in the hypothalamus (miR-207, miR-219–1, miR-212) (McKibben and Dwivedi 2021). After the period of environmental enrichment, an increase in the expression of miR-221 and miR-483 was observed in the prefrontal cortex (Gomez et al. 2015), and a reduction in the expression of miR-92a-3P and miR-134 was observed in the hippocampus (Gomez, et al. 2015). No differences were observed in the expression of miR-207,

Table 3 Impacts of environmental enrichment on epigenetic modifications in brain tissues under adverse conditions

Author, Year	Adverse condition	Brain tissue	miR-expression	Histone modifications	DNA alterations	Summary of the effects of EE on epigenetic processes under adverse conditions
Córneo et al., 2022	Diseases and trauma (Sepsis)	Hippocampus	–	↔HAT, ↓ HDAC	↓ DNMT	EE decreased HDAC and DNMT activity, and protects against neuroinflammation and cognitive damage
Gomez et al., , 2015	Substance exposure (Nicotine)	Prefrontal Cortex	↑ miR-221, ↑ miR-483	–	–	EE upregulated miR-221 and miR-483 and attenuates nicotine-induced increases in pERK1/2 and pCREB
Ji et al., 2023	Psychological stress (CUMS)	Hippocampus	↓ miR-92a-3p	–	–	EE decreased miR-92a-3p and protects damage to behavior and cognition through KLF2 pathway
Koseki et al., 2011	Substance exposure (PCP)	Prefrontal Cortex	–	↑ H3 acetylated at Lys, ↓ HDAC5, ↔ HDAC1	–	EE prevented behavioral damage by reversing the reduction in histone H3-positive cells and the increase in HDAC5 protein expression
Lin et al., 2020	Diseases and trauma (Stroke)	Cortex	–	↓ HDAC2	–	EE reversed upregulation of HDAC2 and promoted functional recovery after the damage
Mckibben et al., 2021	Psychological stress (Early Life Stress)	Hypothalamus	↑ miR-29b-1-5p, ↑ 301b-3p, ↑ -3065-5p	–	–	EE reversed downregulation of miR-29b-1-5p, miR-301b-3p, and miR-3065-5p, and improved behavior through MAPK signaling pathway
Min et al., 2022	Diseases and trauma (POCD)	Cortex, Hippocampus	–	Cortex: ↔H3 (acetyl K14), ↔H4 (acetyl K15), ↔HDAC. Hippocampus: ↑ H3 (acetyl K14), ↑ H4 (acetyl K15), ↓ HDAC	–	EE upregulated H3 (acetyl K14), H4 (acetyl K15), reduced HDAC in hippocampus, and attenuated post-surgical effects through Neuroglia 1 pathway
Orock et al., 2021	Psychological stress (WAS)	Amygdala	–	↑ H3K9 acetylation at GR promoter, ↓ H3K9 acetylation at CRH promoter	–	EE modulated H3K9 acetylation at GR and CRH promoter, and prevented changes in expression of glucocorticoid receptor and corticotrophin-releasing hormone

Table 3 (continued)

Author, Year	Adverse condition	Brain tissue	miR-expression	Histone modifications	DNA alterations	Summary of the effects of EE on epigenetic processes under adverse conditions
Seo et al., 2021	Psychological stress (CUS)	Hippocampus	–	↑ Acetylated H3, ↓ HDAC5, ↑ H3K4me3, ↓H3K27me3	–	EE prevented cognitive damage through acetylation of H3 and H3K4me3, and reducing the level of HDAC5 and H3K27me3
Shen et al., 2019	Psychological sress (CUMS)	Hippocampus	↓ miR-134	–	–	EE upregulated miR-134 and reverses several damages through SIRT1 and BDNF pathway
Wang et al., 2016	Diseases and trauma (Stroke)	Forebrain, Hippocampus	–	Forebrain and Hippocampus: ↑ Acetylated H3, ↔ Acetylated H4;	–	EE upregulated H3 acetylation in forebrain and hippocampus, and attenuated cognitive damage through cholinergic circuits
Wu et al., 2016	Dietary conditions (High fructose)	Hippocampus	–	↓ Nuclear HDAC4, ↔HDAC5	–	EE decreased nuclear HDAC4 levels and prevented cognitive function through BDNF pathway
Xin W et al., 2018	Diseases and trauma (TBI)	Prefrontal cortex	–	↑ H3 acetylation, ↔H4 acetylation	–	EE unregulated H3 acetylation at ChAT gene promoter, and attenuated cognitive damage through CREB and cholinergic pathways
Yu et al., 2020	Substance exposure (Sevoflurane)	Hippocampus	–	↑ Acetylated H3, ↑ Acetylated H4, ↓ HDAC2; ↓ HDAC3	–	EE upregulated H3 and H4 acetylation, reduced HDAC2 and HDAC3 levels, and attenuated cognitive damage through BDNF pathway

CUS Chronic unpredictable stress; *CUMS* Chronic unpredictable mild stress; *DNMT* DNA methyltransferase; *HAT* histone acetylase; *H3K4me* Trimethylation of H3K27me; *H3* Trimethylation of H3K; *4H3K4* histone H3 lysine 4; *HDAC* histone deacetylase; *HDAC1* histone deacetylase 1; *HDAC1* histone deacetylase 2; *HDAC3* histone deacetylase 3; *HDAC5* histone deacetylase 5; *mir* microRNA; *POCD* Postoperative cognitive dysfunction; *TBI* traumatic brain injury; *WAS* Water avoidance stress. ↑ Significant Increased; ↓ Significant Decrease; ↔Non-significant differences

miR-219–1, and miR-212 in the hypothalamus (McKibben and Dwivedi 2021).

Impact of Environmental Enrichment on the Levels of Enzymes Related to Histone and DNA Modifications

The presence of histone modifications was observed in ten articles. After environmental enrichment, in the hippocampus, there was a reduction of HAT (Córneo et al. 2022), HDAC/HDAC4 (Córneo et al. 2022; Wu et al. 2016; Min et al. 2022) in conditions of sepsis, POCD, and high fructose intake. On the other hand, an increase in H3 (acetyl K14), H4 (acetyl K15) (Min et al. 2022), H3K4me3, K3k27me3 (Seo et al. 2021), and HDAC2/3/5 (Yu et al. 2020; Seo et al. 2021) was observed under conditions of POCD, CUMS, and sevoflurane exposure.

In the cortex, there was a reduction of HDAC2 in stroke condition (Lin et al. 2020); in the prefrontal cortex, there was an increase in H3 acetylated at Lys in PCP exposure (Koseki et al. 2012); and in the amygdala, there was a reduction in H3K9 acetylation at the CRH promoter and an increase in H3K9 acetylation at the GR promoter in WAS condition (Orock et al. 2021). There were no changes to the other areas and markers. Only one study observed changes in DNA (Córneo et al. 2022). Córneo et al. (2022) observed that after environmental enrichment and with the sepsis model, there was a reduction in DNMT in the hippocampus of Wistar rats (Fig. 2).

Discussion

The present systematic review aimed to evaluate the impacts of environmental enrichment on the modulation of epigenetic processes in different specific regions under adverse conditions. In this sense, we demonstrated that benefits produced by EE in the brain and animal behavior are directly related to the modulation of epigenetic mechanisms, particularly the modulation of histones toward a more acetylated profile, which results in a chromatin that is more permissive to the transcription machinery of genes associated with cell growth, development and maturation, as well as neuroplasticity in adverse environmental conditions.

The term 'epigenetics' is currently used to describe the study of mechanisms that cause heritable changes in gene expression and cellular phenotype, without any alteration to the sequence of nucleotide bases in DNA. These mechanisms, 'above genetics,' are responsible for modulating genomic structure and activity in response to external and internal cellular signals, thereby playing an essential role in the regulation of diverse cellular processes, including cell development and differentiation (Haig 2004; DeAngelis et al. 2008; Gonzalo 1985). At present, there are three principal epigenetic mechanisms that have been subjected

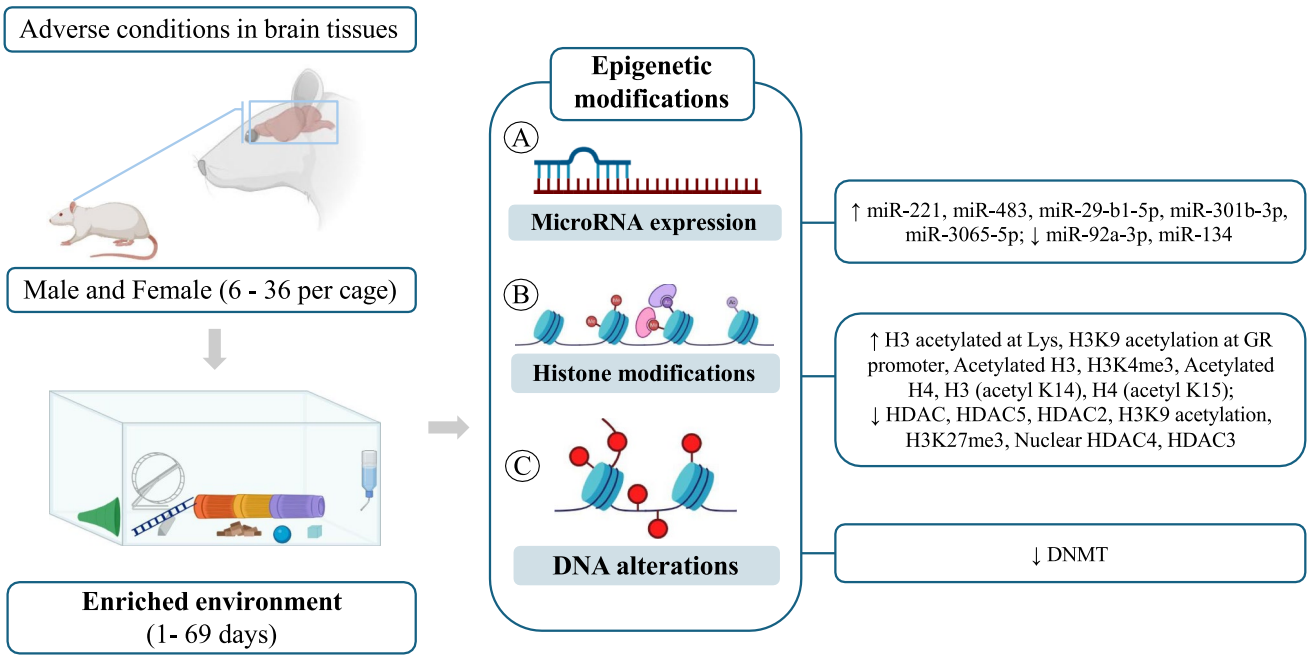


Fig. 2 DNA methyltransferase; HAT: histone acetylase; H3K4me: Trimethylation of H3K27me; H3: Trimethylation of H3K4H3K4: histone H3 lysine 4; HDAC: histone deacetylase; HDAC1: histone deacetylase 1; HDAC1: histone deacetylase 2; HDAC3: histone deacetylase 3; HDAC5: histone deacetylase 5; mir: microRNA

to substantial molecular investigation: DNA methylation, post-translational modifications of histones, and gene silencing through non-coding RNAs, mainly microRNAs (Kim et al. 2009).

Briefly, during the process of DNA methylation, a methyl-CH_3 radical is incorporated into a CpG dinucleotide through the activity of DNA methyltransferases (DNMTs), which typically results in the silencing of the associated gene (Lovrečić et al. 2013; Labbé et al. 2016). In contrast, post-translational histone modifications encompass a range of modifications occurring in the N-terminal tail of chromatin proteins. Histones can be modified through enzymatic processes of acetylation and methylation, which are more fully described in the literature, or through ubiquitination and phosphorylation. These modifications regulate chromatin packing and, as a result, affect the transcriptional activity of the chromatin itself (Qureshi and Mehler 2018; Kouzarides 2007). Finally, the process of gene silencing through microRNAs has been described more recently and consists of a combination of steps involving translational repression and degradation of the target mRNA (Jonas and Izaurralde 2015).

Given its dynamic nature, the epigenetic profile, along with its modifications, orchestrates gene expression and function at botch cellular and tissue levels. Furthermore, it mediates the interactions between genes and the external environment, from the development through to the cellular aging. Consequently, over the past decades, there has been a growing interest in the impact of epigenetic modifications across various fields of neurobiology, aiming to elucidate gaps in our understanding of topics such as learning and memory, as well as onset and progression of several psychiatric and neurological disorders (Praag et al. 2000; Anier and Kalda 2012).

As an example of external factors, environmental enrichment (EE) was first described by Donald Hebb (1949) and refers to simple strategies for manipulating standard laboratory housing conditions, with the aim of promoting neurorehabilitation by optimizing the diversity, quality, and intensity of environmental stimuli (Ball et al. 2019; Kempermann 2019). In general, animals maintained in EE are provided with larger living spaces, a variety of toys and other stimulating items (such as sound, light, and colors), periodic changes in food and water, and increased opportunities for physical activity and social interaction (Yu et al. 2014). Given the well-established impact of environmental conditions during childhood and adolescence on adult neuroplasticity, some researchers have recently sought to elucidate the role of epigenetic mechanisms in modulating behavioral, cognitive, and neurological performance in response to positive and/or negative stimuli (Lehmann and Herkenham 2011; Volkers and Scherder 2011).

Thus, the aim of this study was therefore to carry out the first systematic review of the influence of epigenetic mechanisms on the well-described impact of different EE protocols on the brains of rodents exposed to favorable or unfavorable environmental conditions. In a translational context, the elucidation of these mechanisms can contribute to the discovery of potential molecular targets through simple methods of non-pharmacological interventions for different pathologies and neuropsychological disorders.

Among the 14 studies selected here, 10 showed that the benefits promoted by EE protocols in young rodents' brains exposed to different adverse conditions involve post-translational modifications of histones, usually acetylation or deacetylation process.

Consistent with existing literature, Lin et al. (2020) demonstrated that the upregulation of histone deacetylase 2 (HDAC2), a negative regulator of neuroplasticity, following a stroke in C57BL/6 mice, could be reversed with a 6-day environmental enrichment protocol. The reduction in HDAC2 in response to EE also resulted in the expression of neurotrophins and proteins associated with neuroplasticity, thereby contributing to the functional recovery of the cortex. Importantly, the HDAC2 knockdown mimicked the benefits promoted by EE, which reinforces that epigenetic modification of histones through HDAC2 is a critical step in recovery after damage. Similarly, Wang et al. (2016a, b) revealed that cognitive recovery of Kunming mice under EE conditions after stroke involves the maintenance of acetylation homeostasis in cholinergic pathways. In this study, 28 days of exposure to an EE partially reversed the reduction in acetylated histone levels in cholinergic cells of the forebrain and hippocampus in mice with post-damage cognitive impairment. Notably, there was a significant increase in Ac-H3 levels in both regions, impacting the cascade of acetylcholine neurotransmitter, which is essential for cognitive function. Later, they demonstrated that EE's ability to alleviate working memory impairment symptoms after traumatic brain injury also involves increasing Ac-H3 levels in the cholinergic system in the prefrontal cortex region of these mice (Wang et al. 2018). Similarly, C57BL/6 mice that were maintained on preoperative EE demonstrated resistance to post-surgical cognitive dysfunction, with the preservation of neuroglia 1 and an improvement in memory and learning. These benefits of EE were associated with the maintenance of homeostatic levels of HDAC activity and Ac-H3 and Ac-H4 in the hippocampus of these animals (Min et al. 2022).

Furthermore, 2 of the 10 studies selected for review on the role of histone modifications in the benefits of EE were conducted in models of mental and behavioral disorders. Seo et al. (2021) demonstrated that keeping C57BL/6j neonates in EE with racing wheels, tunnels, balls, and blocks prevents chronic stress and depressive behavior when they become adults. They demonstrated that these effects of postnatal EE

are due to an increase in the level of Ac-H3 of the p11 gene in the hippocampus, a reduction in HDAC5 activity, as well as the prevention of stress-induced changes in the trimethylated state of histone H3 lysine 4 (H3K4) and H3K27. A study conducted on female Fischer-344 rats demonstrated that the stress-relieving effects of the short-term EE protocol in the brain-intestinal axis are due to the maintenance of histone H3 lysine 9 (H3K9) acetylation in specific promoters of the central nucleus of the amygdala.

The preservation of the epigenetic state resulted in a reduction in visceral and somatic nociception over the long term (Orock et al. 2021). In addition, Koseki et al. (2012) reported that a 4-week exposure to EE, using a variety of inanimate objects during adolescence, can prevent the development of schizophrenic behaviors in ICR mice. This effect was associated with increased levels of histone H3K9 acetylation and reduced HDAC5 activity in the prefrontal cortex of animals exposed to phencyclidine (PCP), a non-competitive antagonist of the *N*-methyl-D-Aspartate (NMDA) receptor.

Given the extensive literature on the impact of maternal drug use or nutrition on fetal neurodevelopment, Yu et al. (2020) investigated the role of histone modifications in the offspring of rats exposed to 2.5% sevoflurane. Additionally, they examined whether 2 days of EE could mitigate the epigenetic changes and cognitive impairment associated with this exposure. In this study, EE with plastic tunnels, wheels, and balls, among other toys, was effective in alleviating behavioral impairment in the offspring of rats exposed to 6 h of 2.5% sevoflurane. These effects were associated with a significant increase in the level of Ac-H3 and Ac-H4, a reduction in HDAC2 and HDAC3, as well as cognitive improvement associated with BDNF signaling in the pups' hippocampus. Similarly, EE with plastic toys and nesting material was observed to reduce the activity of nuclear HDAC4 in binding to promoters II and IV of the *bdnf* gene, which resulted in improved learning and memory in the offspring of females fed a high-glucose diet during gestation and lactation (Wu et al. 2016).

In the present systematic review, a total of four studies were selected regarding the potential of EE to improve neurobiological aspects through the modulation of microRNAs. An analysis of the hippocampus of Sprague Dawley rats with depressive behavior induced by mild stress revealed that the 3-week EE intervention protocol was effective in reducing the level of miR-92a-3p, which has been previously described as elevated in patients with depression and anxiety associated with substance abuse (Ji and Zhao 2023; Chen et al. 2021). In another study, the same protocol was also found to improve symptoms of chronic stress, depressive behavior, and cognitive deficits through the regulation of the SIRT1/mirR-134 signaling pathway by reducing the level of miR-134 and thus increasing the availability of its target SIRT1, which is necessary for greater BDNF expression and neuroplasticity (Shen et al. 2019).

Furthermore, rats in EE also showed a lower sensitivity to motor damage induced by nicotine abuse through an increase in 6 different microRNAs, mainly miR-221 and miR-483, compared to those kept in impoverished or standard environments. Interestingly, the differential expression screening conducted by McKibben and Dwivedi (2021) revealed that early life stress increases susceptibility to depressive behavior in adults by modulating the microRNA profile. In the analysis of the hypothalamus of rodents subjected to maternal separation, 29 microRNAs were upregulated while 21 were downregulated. In the group of downregulated miRNAs, the level of 3 specific miRNAs (miR-29b-1-5p, -301b-3p, and -3065-5p) exhibited a notable increase following the EE intervention, aligning with the control without stress. As expected, the modulation of these miRNAs also altered the expression of the respective target genes, such as MAPK6 and MMP19.

Among the articles reviewed in this study, only one examined the correlation between EE and DNA methylation. In this context, Córneo et al. (2022) demonstrated that intervention with EE protects against cognitive impairment induced by neuroinflammation through the repression of the hypermethylated state induced by both HDACs and DNMTs in a mouse model of sepsis. In summary, the studies discussed here demonstrate that the cognitive benefits of EE are linked to its capacity to modulate key biological processes in the animal brain. In different models, EE stimulation was able to protect the brain against adverse conditions at a "pre-transcriptional" level by preserving the acetylation profile. This was achieved by reversing the deacetylated or hypermethylated state of histones and DNA, respectively, or by promoting the activity of histone acetyltransferases. In addition, stimulation with EE was also effective in regulating these processes at the “post-transcriptional” level, by modulating the activity of microRNAs and, consequently, their respective target genes. The modulation of these mechanisms revealed the potential of EE to control the production and/or availability of neurotrophins and genes involved in the process of neurogenesis and neuroplasticity.

Limitations

Some limitations can be observed in the present review. Firstly, the heterogeneity of the epigenetic markers used in the included studies makes it difficult to observe the modulation of a specific potential target in the brain in response to environmental enrichment under adverse environmental conditions. This would require a more in-depth investigation not just of a single marker, but of an entire signaling pathway that may be activated/inactivated. Secondly, only one study included analyzes the impacts of environmental

enrichment on DNMT activity. This enzyme participates in regulatory mechanisms, including molecular interactions, post-translational modifications, alternative splicing, and gene duplication or loss. Furthermore, the molecular functions of DNMTs are not limited to gene silencing and may also include transcriptional activation and transcriptional post-regulation. Finally, resolving these limitations can help in the discovery and establishment of new knowledge within molecular genetics and neuroscience, opening an effective field of possibility for translational studies with human beings with diverse chemical, pharmacological, pathological, and lifestyle-related exposures.

Future Directions

The evidence presented in this systematic review demonstrates a new frontier of scientific knowledge, pointing to environmental enrichment as a tool capable of modulating epigenetic processes mainly responsible for controlling gene expression in the central nervous system. These mechanisms may help future research to discover fundamental signaling pathways for the regulation of cognitive, behavioral, and neuroplasticity processes and can be applied in favorable and adverse environmental contexts. Next, it is necessary to develop translational studies that apply this non-pharmacological tool in pathologies that affect the central nervous system, including multiple sclerosis, Parkinson's, and Alzheimer's, which are known to be effectively regulated by epigenetic processes. Finally, environmental enrichment protocols should be standardized to avoid heterogeneity of methodology and results.

Conclusions

In summary, we have shown that the benefits of EE on the animal brain and behavior are directly related to different epigenetic mechanisms, particularly the modulation of histones toward a more acetylated profile, which results in a chromatin that is more permissive to the transcription machinery of genes involved in cell growth and neuroplasticity. In this sense, interventions based on positive environmental stimuli, such as EE, are emerging as non-pharmacological, low-cost, and simple-to-apply alternatives for preventing or mitigating symptoms in various disorders affecting the brain. This was the first systematic review on the subject, contributing to a detailed analysis of each EE protocol, the animal model studied, and the main effects achieved, finally advancing the standardization of the strategy for clinical application.

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Declarations

Conflict of interest The authors declare no competing interests.

Animal Ethics and Consent to Participate declarations Not applicable.

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