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Review Article

Pathophysiological Mechanisms of Maternal Separation Stress in Cognitive Dysfunction

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ABSTRACT Maternal separation (MS) animal stress models are commonly used to evaluate the factors affecting cognitive development. These models simulate mother–offspring separation during the lactation period because it is the most critical neurodevelopmental period for exploring the impact of early-life adversities on the risk of various neurological and cognitive disorders that can occur during adulthood. Cognitive dysfunction may result from multiple contradictory mechanisms that have not yet been reviewed. Therefore, in this narrative review, we aim to offer a critical and objective review of studies published in databases, such as PubMed, Google Scholar, and Web of Science, over the last 5 years that have used this stress model to propose a pathophysiological mechanism of MS-induced cognitive dysfunction. Our review reveals that MS induces cognitive dysfunction via the hypothalamic–pituitary–adrenal axis, which may alter neurogenesis and/or apoptosis. Furthermore, MS leads to neuroinflammation, oxidative stress, mitochondrial dysfunction, and accumulation of neuronal aggregates. In conclusion, the MS stress model offers a cost-effective method to evaluate potential therapeutic agents for a variety of neurodegenerative and neuropsychological disorders. Integrating multidisciplinary research into assessments is a comprehensive strategy for the early prevention of these disorders, which is one of the main objectives of the Saudi Arabia 2030 vision for efficient child integration in society.

Keywords: Hippocampus, Maternal Separation, Cognitive Dysfunction, Neuroinflammation, Oxidative Stress.

INTRODUCTION

Early-life adversities increase the risk of developing neurodegenerative, neuropsychological, depressive, and anxiety disorders [1]. Maternal presence during the early postnatal period is crucial for cognitive development, and depriving offspring of maternal care is a powerful early stress model commonly used to study factors affecting cognitive development [2]. This animal model of maternal separation (MS) induces stress by separating newborns from their mothers during the early postnatal period, with a time period ranging from 15 min to several hours, to induce neurological complications at the genetic and molecular levels [3]. MS during the early postnatal period can lead to long-lasting memory disorders, learning disabilities, and cognitive dysfunction due to hippocampus impairment [4]. Determining the effects of MS on cognitive dysfunction is challenging due to numerous variables, including stress patterns, age at stress induction, and stress duration and intensity [5]. Additionally, the combination of MS with other stress modalities obscures the pathophysiological mechanisms underlying the negative outcomes of MS. Despite the widespread use of animal models of MS in neurodevelopmental research, studies elucidating the pathophysiological mechanisms of MS-induced cognitive dysfunction are scarce. Furthermore, the differential outcomes of various factors, such as age at stress onset, sex-specific outcomes, and interactive neurological pathways, can lead to variable results. Therefore, through this narrative review, we aim to offer a comprehensive, critical, and objective review of the literature and identify studies that have used MS animal models to understand the pathophysiological mechanisms induced by MS that lead to cognitive dysfunction.

Inclusion/exclusion criteria: The databases of PubMed, Google Scholar, and Web of Science were searched for articles published in the last 5 years that used the MS animal stress model to propose a pathophysiological mechanism of MS-induced cognitive dysfunction. We

included papers that presented MS outcomes with respect to brain structures responsible for cognitive function, mainly the hippocampus, amygdala, prefrontal cortex (PFC), and dentate gyrus (DG). Studies that used the MS model to explain non-neurological outcomes were excluded. Older studies were included only if they showed distinctive results that no other studies had proposed regarding the pathophysiological mechanisms of MS. Therefore, this review is divided into sections to illustrate how MS affects cognitive and behavioral functions, specifically focusing on the hypothalamic–pituitary–adrenal (HPA) axis and important hippocampal physiological processes such as neurogenesis, programmed cell death, and apoptosis. It also includes sections explaining how MS might lead to neuronal inflammation, oxidative stress, mitochondrial dysfunction, and accumulation of harmful neuronal aggregates.

PATHOPHYSIOLOGICAL MECHANISM 1: MS AND HPA AXIS

Postnatal MS can affect neuroendocrine physiological responses to stress, potentially disrupting activities of the HPA axis [6]. Prevention of chronic glucocorticoid (GC) exposure protects the developing brain from the hyperactive HPA axis due to increased corticotropin-releasing hormone (CRH) signaling and disturbed negative hormonal feedback [7,8]. Gender differences can be observed in MS, altering glucocorticoid receptor (GR) and mineralocorticoid receptor expression, such as Npas4 and nuclear receptor subfamily 1 group D member (Nr1d1), in the hippocampus and PFC [9]. A previous study revealed that a periodic 3-h MS affected hippocampal CRH gene expression and baseline HPA axis activity at different time periods from the sixth postnatal day (PND), ultimately affecting cognitive function [8]. Even a single 24-h MS negatively impacts the behavior and cellular functioning of the bed nucleus of the stria terminalis CRH cells [10]. MS amplifies excitatory postsynaptic currents and reduces M-currents, which are crucial for maintaining membrane potential. It also increases the levels of CRH and pituitary adenylyl cyclase-activating cells, which are responsible for upstream CRH activity [11]. Extended MS significantly affects spatial working memory owing to increased corticosterone levels and neuronal loss in the DG [7]. Persistent memory impairment becomes evident during adulthood, even though GC, brain-derived neurotrophic factor (BDNF) receptor, or tropomyosin receptor kinase B levels are not impacted [12].

When combined with other stressors, MS may cause dysregulation of the HPA axis function and GR expression and lead to behavioral changes in both mothers and offspring. After weaning, MORC Family CW-Type Zinc Finger 1 (Morc1) expression decreased 4 h after MS in mothers, whereas the expression of GR, nuclear receptor subfamily 3 (Nr3c1), remained unaffected. Levels of serum gamma-aminobutyric acid (GABA), but not glutamate, were significantly increased, supporting subclinical indicators of postpartum depression [13]. HPA axis dysfunction can also be attributed to the restriction of pub-mother nutritional needs, which impacts cognitive well-being and causes oxidative stress through hyperactivity of the HPA axis [14]. A 3-h MS combined with restricted bedding leads to anxiety-like behaviors and increased hypothalamic CRH levels [15]. Six hours of MS with limited bedding leads to an upregulation of the CRH gene, with modification of stress response genes, resulting in increased expression of CRH receptor 1, CRH receptor 2, and serotonin receptor 5-hydroxytryptamine-1A, and decreased expression of Nr3c1 and Htr1a in the hippocampus [16]. In contrast, comparing a single 24-h MS trial with a chronic 3-h MS trial showed no effects on the expression of stress-related CRH, CRH receptor 1, CRH receptor 2, Nr3c1, Nr3c2, and serum corticosterone at the end of the second postnatal week in the DG [17]. Twenty-four-hour MS lowered the expression of catechol-o-methyl transferase, which is involved in regulating GCs. Increased numbers of glutamic acid decarboxylase 67-positive neurons were found in the DG, hippocampus cornu ammonis (CA3), CA1, subiculum, presubiculum, and parasubiculum. Further, there were also more parvalbumin-positive cells in all areas except the CA1 [3]. Notably, a single MS trial on the third PND elevated BDNF expression in CRH neurons, suggesting a heightened level of neural plasticity [18]. MS reduces responses in the novel object recognition task by lowering the expression of Nr1d1 in the dorsal hippocampus [19].

MS can also affect adult learning and memory by disrupting developmental shifts in GR expression, which typically decreases during the second and third postnatal weeks, but 1 h of MS slows down this reduction and increases GR expression during weaning [20].

GR is found in the cytoplasm with a group of proteins, including FK506-binding proteins 51 and 52, which promote affinity and facilitate action via microtubule-protein interactions. However, 4 h of MS treatment increases mRNA expression in the amygdala and hippocampus [21]. Moreover, mice exposed to MS show increased repressive methylation of the GR exon 17 promoter and decreased histone acetylation, indicating long-lasting negative effects on behavior due to postnatal MS histone modification [22]. c57BL6 mice exposed to MS and social defeat stress showed that both stressors significantly influenced genes involved in histone methylation, opioids, neurotrophins, and GC signaling pathways, suggesting potential molecular mechanisms for cognitive and behavioral regulation [23]. Quantitative polymerase chain reaction results revealed that 3 h of MS caused variations in the expression of transcripts associated with GC signaling, a significant reduction in the Fkbp5 transcript, and an elevated Ptges3 transcript [18]. Females showed more Fos-labelled neurons than males; however, these findings cannot be solely attributed to MS, as they were observed under combined stressors [24]. Generally, combining MS with other stress methods may be useful to mimic specific disease conditions; however,

this makes it more difficult to understand the specific adversities of the MS stress model itself.

Now that we have discussed the effects of HPA axis dysfunction caused by MS, we can examine how it affects neurogenesis, since it has been suggested that this dysfunction can directly disrupt normal neurogenesis.

PATHOPHYSIOLOGICAL MECHANISM 2: MS AND NEUROGENESIS AND APOPTOSIS

Neurogenesis is a neuronal physiological process that involves different stages of formation of new neuronal cells and is believed to occur throughout life in the DG of the hippocampus. The postnatal development of the hippocampus involves extensive neurogenesis, synaptogenesis, myelination, and microglial maturation [25]. Increased vulnerability to cognitive impairment in adulthood may result from aberrant adult neurogenesis, hypomyelination, or oligodendrocyte dysfunction [26]. An increase in CRH during critical periods causes poor dendritic branching, reduced myelination, and neuronal conductance owing to the HPA axis feedback deficit [10]. Corticosterone cytotoxicity induced by 15-min MS increases the risk of hippocampal abnormalities due to decreased neurogenesis or increased neuronal apoptosis in the CA3 region of the hippocampus [9]. Corticosterone cytotoxicity mediates apoptosis by activating protein kinase A, protein kinase C, calcium/calmodulin-dependent kinase II, and extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) [27]. In addition, postnatal MS inhibits neural stem cell proliferation, impairs survival, and alters newborn cell fate in the DG [60]. Even short-term MS can significantly reduce synaptosomes and increase the number of immature spines in the CA1 region of 1-month-old mice. Moreover, it affects synaptic maturation in juvenile mice by decreasing protein production for axonal growth and myelination [28]. Daily 3 h of MS impacts hippocampal granule cell neurogenesis; however, its impact on the neurogenic niche remains uncertain [56]. Based on a previous study that showed reduced hippocampal volume due to impaired synaptic plasticity, 6 h of MS led to enlarged gray matter volume in the amygdala on magnetic resonance imaging in late adulthood, but not in early adulthood or immediately following MS [29]. Three hours of MS affected locomotor activity, spatial memory, and recognition memory due to a reduced neuronal count in the hippocampus, as evaluated by the mean number of cells expressing doublecortin and Ki67 [30]. MS reduced dorsal hippocampal neurogenesis only in young adults, while 10-month-old mice exhibited a similar decline in dorsal and ventral hippocampal neurogenesis. These findings were attributed to MS-induced insulin sensitivity [31]. Further, expression of the excitatory neurotransmitter N-methyl-D-aspartate receptor subunit GluN1 decreased with an increase in the quantity and diameter of dark neurons in CA3, suggesting MS-induced neuronal loss [32].

At the end of the second postnatal week, MS-induced changes in gene expression are associated with myelin-ensheathment genes in the medial PFC [33]. In addition, western blot analysis has revealed that adult anxiety-like behavior is related to persistent atypical DNA methyltransferase changes in the hippocampus of MS-exposed mice [34]. Further research is required to determine whether brief MS indirectly inhibits myelination or spontaneous firing activity [35]. The glial cell phenotype analysis showed that MS increased DG proliferation in females to a greater extent than that in males [36]. Asymmetrical synapses with a thicker postsynaptic density than that of the presynaptic fraction facilitate hippocampal plasticity. In rat models of depression exposed to MS for 3 h, presynaptic density and cleft length were reduced [37].

In contrast, MS improved learning and memory and increased dendrite length, terminal tips, and spine density, particularly in thin spines, as evidenced by electroporation, three-dimensional reconstruction, immunohistochemistry, and BrdU labeling [38]. Additionally, MS increased the number of undeveloped DCL neurons in mice lacking the methyl-CpG-binding protein gene, which regulates gene expression and neuronal plasticity [39]. Interestingly, this effect was not evident in females heterozygous for methyl-CpG-binding protein, who showed less anxiety-like behaviors [40]. This study revealed a reduction in reelin levels in mutant rats for the first time [39]. The opposing effects of MS on the hippocampus could be influenced by the age of onset as well as by various brain regions and the variability of staining methods.

MS can affect neurogenesis through Ca^{2+}-binding proteins. For instance, MS reduces the density of interneurons expressing the Ca^{2+}-binding proteins parvalbumin, calbindin, and calretinin in the amygdala and nucleus accumbens [41]. A study found that 3 h of MS reduced exploratory behaviors among males and caused spatial memory loss in both males and females; however, calretinin and calbindin-D28k levels differed between sexes [42]. MS led to increased arginine vasopressin expression and decreased levels of GABAergic interneuron markers, including parvalbumin, and calbindin-D28k. A reduction in cortical Ca^{2+}-binding protein-28k-positive cells and an increase in cortical ionized Ca^{2+}-binding adaptor-positive cells was observed, confirming the early-life stress paradigm [6]. A study involving MS and calbindin-D28K in the hippocampus found a significant increase in these substances and a reduction in the medial basal hypothalamus, indicating a dysfunctional negative feedback of the HPA axis [43]. Although this study did not meet the inclusion criteria in terms of publication year, it is the only study to demonstrate the effect of MS on calbindin-D28K in the hippocampus. Besides, 24-h MS reduced the number of parvalbumin-expressing interneurons in the CA1 and PFC and reelin-expressing interneurons in the CA1 and CA3 regions of the hippocampus. However, cellular apoptosis did not show any effect, suggesting the downregulation of markers rather than the depletion of interneurons.

Immunohistochemistry targeting glutamatergic and inhibitory vesicular transporters showed reduced inhibitory synapses in the CA1 and CA3 areas; however, excitatory synapses remained unaltered. Therefore, modifications to the inhibitory circuitry caused by MS appear to be cellular and region-specific [44].

MS for 1 h postnatally reduced microglial ramifications, led to poor phagocytosis of synaptic debris, and decreased the expression of receptors known as triggering receptors expressed on myeloid cells-2. Elevated phagocytic activity has been linked to increased spine density in the CA1 pyramidal neurons, suggesting that adequate hippocampal stimulation between the second and third weeks of infancy is crucial for microglial ramification and synaptic pruning, which can affect hippocampal function and neuronal connectivity [45]. The physiological transformation of ameboid microglia into ramified microglia is impaired by early-life stress in a region-dependent manner. Antibodies against NeuN, microglia, Ki67, and doublecortin have shown that the MS group has more Ki67-positive cells in the DG and larger densities of ameboid and intermediate microglia in the PFC [17].

Normal hippocampal development relies on apoptosis or programmed cell death, which can be affected by the adverse effects of MS [46]. MS may lead to medial PFC apoptosis; however, the mechanisms underlying this effect are unclear [47]. Growing evidence suggests that the autophagy–lysosomal pathway can lead to increased protein deposition and neurodegeneration [48]. MS alters the autophagy–lysosomal pathway, potentially dysregulating proteostasis and affecting the onset and progression of neurodegenerative diseases [48]. Three hours after MS, learning and memory retrieval are impaired by increased apoptotic cell death and decreased early-phase protein kinase B (AKT) phosphorylation in the DG region. During adulthood, MS rats show lower GR1 expression in the DG, suggesting that behavioral alterations may link MS-induced pathological alterations to the inhibition of the AKT pathway and neuronal apoptotic death [49]. Analysis of hippocampal neuronal death in MS-induced depressive behavioral changes showed increased mRNA levels of Bax, caspase-3, and caspase-9 and decreased expression of BCL-2 and BDNF. However, these changes were reversed by treatment with a mitogen-activated protein kinase inhibitor. This study suggests that the death of hippocampal neurons may be mediated by the ERK1/2 signaling pathway, potentially opening new treatment options for neurodegenerative disorders [50]. The Majcher–Maślanka study revealed that MS rats had more numbers of astrocytes and NG2 glial cells but fewer microglial cells. Proapoptotic gene expression was lowered, whereas pro-survival gene expression was increased, suggesting potential interference with neuronal apoptosis [47].

Having discussed the effects of MS on neurogenesis, we now review MS-induced neuronal inflammation.

PATHOPHYSIOLOGICAL MECHANISM 3: MS AND NEUROINFLAMMATION

MS is a reliable model for studying the pathophysiology of mental and behavioral disorders influenced by neuroinflammation. Three hours of MS increased microglial activation in a traumatic brain injury model, indicating increased neuroinflammation but reduced cell proliferation in the ipsilateral neurogenic niche, and impacted the survival of cells in the hippocampus on the same side of the injury [51]. Cognitive behavior was not obviously changed due to MS, but depression-like behaviors increased when they were exposed to secondary adulthood stress. MS increases pro-inflammatory markers, decreases anti-inflammatory parameters, activates microglia, and facilitates pro-inflammatory transitions in the hippocampus. Moreover, changes in neurogenesis and BDNF expression in the hippocampus have been linked to inflammatory processes [52].

Limited research has been performed to understand how early MS and sex affect blood–brain barrier (BBB) function and immune system response to lipopolysaccharide-induced neural inflammation [46,47]. Nicolas et al. studied the effects of MS and lipopolysaccharides on hippocampal neurogenesis and inflammatory responses in juvenile female rats. They discovered that MS increased the levels of the pro-inflammatory cytokine interleukin (IL)-1 in the ventral hippocampus. In contrast, MS lowered microglial activity in both the dorsal and ventral hippocampi. Neither MS nor lipopolysaccharide had an effect on new neuron generation or distal dendrite density [53]. Increased BBB permeability leads to proinflammatory responses in the hippocampus. Separated male pups showed an elevated neuroinflammatory response, whereas separated female pups showed no difference, further suggesting that MS accelerates neurodegenerative onset through neuroinflammation in a sex-specific manner [47]. MS attenuates the activity of prostaglandin-producing enzymes, COX-2, prostaglandin endoperoxide synthase, and chemokines (CXCL-1 and MCP-1), without elevating plasma cortisol levels, leading to increased susceptibility to depressive-like behavior [54]. MS causes depressive-like upregulation of inflammatory genes IL-1β and TNF-α in the hippocampus [55]. Furthermore, MS causes sex-specific variations in chemokine motif ligand 1 and TNF levels as early as the second postnatal week [56]. MS activates microglia in the hippocampus, amygdala, and PFC due to high levels of inflammatory cytokines, especially IL-17 [57]. Changes in the levels of pro-inflammatory cytokines were found to depend on sex and age. A previous study showed that IL-1β and IL-10 levels decreased in 1-month-old animals, whereas IL-4 elevation was observed around 3 weeks postnatally. Thus, circulating cytokine and parvalbumin levels could be used as early signs of cognitive decline in adulthood [58]. However, studies on the effects of MS on these cytokines in MS-induced behavioral deficits are scarce.

MS-induced neuroinflammation affects mitochondrial function, which protects neurons from oxidative stress toxicity. The next section reviews the mechanism by which MS induces mitochondrial dysfunction.

PATHOPHYSIOLOGICAL MECHANISM 4: MS AND MITOCHONDRIAL DYSFUNCTION

Over 100 stress-related proteins were upregulated, whereas almost 140 were downregulated, revealing an enrichment of proteins linked to mitochondrial dysfunction in a MS animal model combined with social isolation or chronic restraint stress [59]. MS models exhibited damage to mitochondrial membrane proteins and lipids, disruption of electron transport chain enzymes, and impaired expression of mitochondrial genes [60]. Fission and fusion are crucial functions of mitochondria. Function is controlled by the fission proteins dynamin-1-like protein (Drp1) and fission-1 (Fis1), whereas fusion is controlled by mitfusin1 (Mfn), Mfn2, and optic atrophy-1 (OPA1) proteins [61]. A 3-h MS model with reduced synaptogenesis and neuronal synapse formation was associated with mitochondrial damage and lowered ATP levels in the hippocampus. MS also affected Mfn2, Drp1, and fission-1 expression. Western blotting revealed reduced Mfn2 expression, whereas the levels of the fission mediators Drp1 and fission-1 were elevated [37].

MS can increase reactive oxygen species levels and mitochondrial respiratory chain complexes I, II, III, and IV and induce depressive behavior with upregulation of glutamate dehydrogenase-1, which is the determinant of mitochondrial energy production, and downregulation of the isocitrate dehydrogenase [NAD] alpha subunit [60]. These enzymatic changes cannot be attributed solely to the MS effect, as they were observed in a chronic mild stress model. A deeper understanding of the MS modification of certain brain parameters is necessary to identify phenotypes and biomarkers linked to mitochondrial dysfunction as prophylactic, diagnostic, and novel therapeutic approaches for cognitive dysfunction.

PATHOPHYSIOLOGICAL MECHANISM 5: MS AND OXIDATIVE STRESS

Long-term exposure to MS can alter the HPA axis and mediate neuroinflammation and oxidative stress, leading to the emergence of neurodegenerative diseases [62]. Three hours of MS in the first 2 postnatal weeks induced depression and anxiety-like behaviors, which were linked to enhanced lipid peroxidation by elevated malondialdehyde (MDA) and nitric oxide levels, as well as a reduction in antioxidant capacity in the brain [14]. Three hours of MS followed by multifactorial stress in adulthood resulted in disturbed cognitive test results, with reduced levels of antioxidative enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPX) and increased MDA levels [63]. Soares et al. employed 4 h of MS in the preweaning period and examined parts of the brain for antibodies against parvalbumin and 8-oxo-dG, which are markers of oxidative DNA damage. They found that 8-oxo-dG and parvalbumin levels were higher in the PFC, basolateral amygdala, and hippocampus in a sex-dependent manner [14]. MS affects the oxidative markers and behavior of adult mice, showing anxiety-like behaviors, as well as long-term lowering of GPX, catalase, and thiobarbituric acid reactive substances [62]. Additionally, low levels of TrkB, nitrite, BDNF, and antioxidant activity have been observed in the hippocampus 3 h after MS [64]. MS extended for 6 h leads to high serum corticosterone and MDA levels and reduced total SOD and GPX levels [65]. The interpretation of these changes cannot be limited to MS alone, because several stress variables were employed in the experimental design. After reviewing the effects of MS on oxidative stress, we explored its effects on the accumulation of toxic aggregates in neurons.

PATHOPHYSIOLOGICAL MECHANISM 6: MS AND ACCUMULATION OF NEURONAL AGGREGATES

Postnatal stress increases the production of amyloid precursor protein (APP) and amyloid-beta (Aβ) peptides, which can change cognitive function. Three hours of MS in APP-wild-type male transgenic mice led to cognitive deficits, as observed in the Morris water maze test, due to higher senile plaques and lower cholinergic neurons in the hippocampus. APP heterozygous mutant mice exhibited significant microglial activation, early Aβ plaque formation, increased vessel-associated microglia, and disruption of the BBB [66]. It has been revealed that Aβ peptides can directly stimulate CRF neurons, increase levels of Aβ 40 and Aβ42, increase expression of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), and phosphorylate Tau in the hippocampus potentially causing accumulation of neuronal aggregates. The combination of MS-induced microglial activation and APP mutation may impede the vascular inflammatory system and accelerate the progression of cognitive dysfunction in a sex-specific manner. MS female mice models showed increased premature Aβ peptides accompanied by changes in BDNF, cytoskeleton-associated protein expression, and microglial activation in the PFC [56].

The following diagram summarizes the main pathophysiological mechanisms of MS.

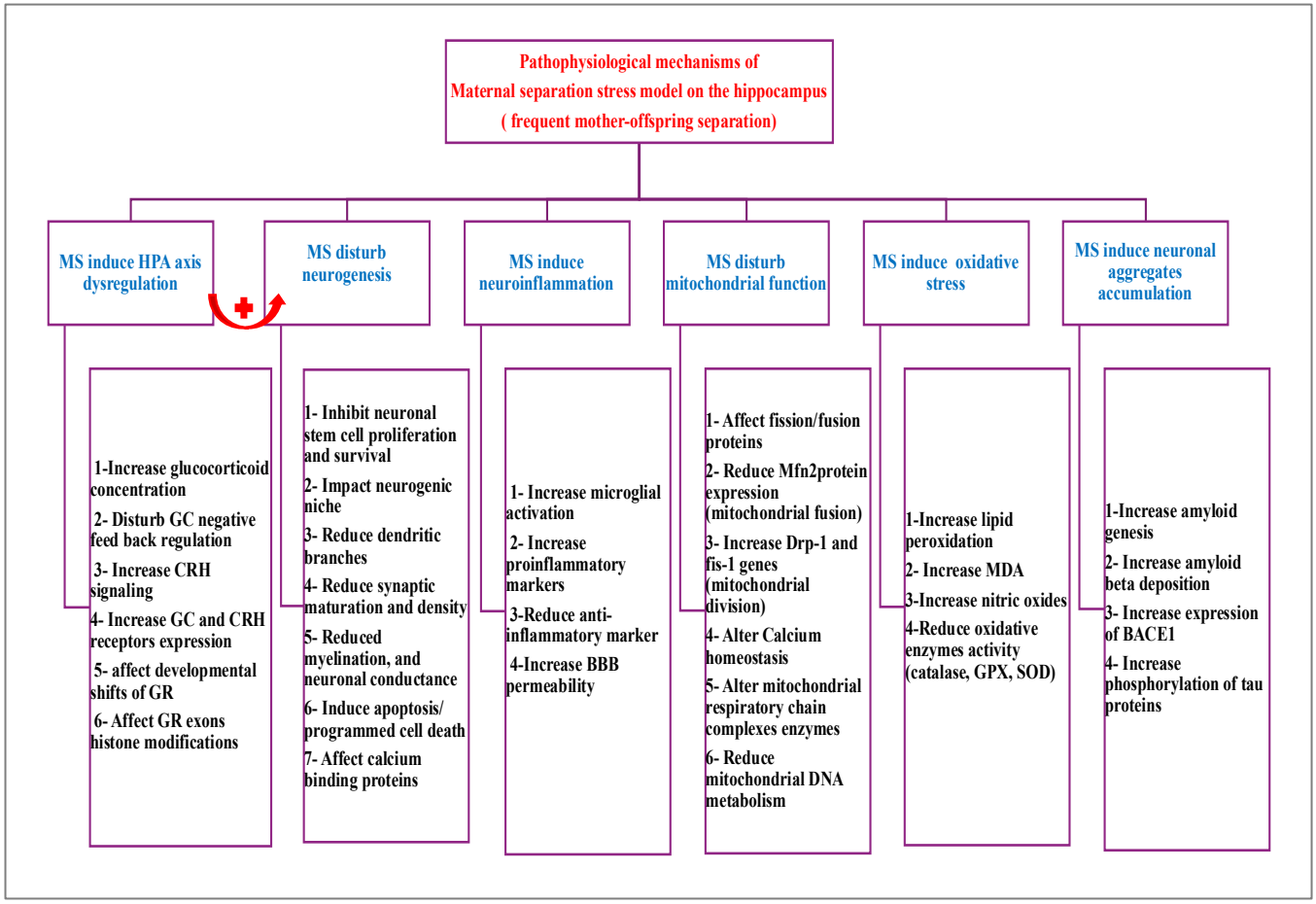

Figure 1: Pathophysiological mechanisms of MS-induced cognitive dysfunctions**.** The figure illustrates the different mechanisms and pathophysiological outcomes of maternal separation. + refers to induce. *MS:* maternal separation *HPA:* hypothalamic- pituitary- adrenal axis *GC:* glucocorticoid *CRH:* corticotropin-releasing hormone *GR:* glucocorticoid receptors *BBB:* blood brain barrier *Mfn2:* mitofusin 2 *Drp-1:* dynamin related protein *MDA:* malonaldehyde *GPX:* glutathione peroxidase enzyme *SOD:* superoxide dismutase *BACE1:* β-site amyloid precursor protein cleaving enzyme.

CONCLUSION

Frequent mother–infant separation during early infancy can lead to neurological alterations and various disorders. MS during the early postnatal period can cause memory disorders, learning disabilities, and cognitive dysfunction owing to impaired hippocampal function. Factors such as sex, age, and MS protocol affect the sensitivity of the hippocampus to stress hormones. Combining MS with other stressors can increase vulnerability to cognitive dysfunction in adulthood owing to hippocampal neurogenesis, inflammatory processes, oxidative disorders, and induced apoptosis. Furthermore, the differential outcomes of various factors, such as age at stress onset, sex-specific outcomes, and interactive neurological pathways, can lead to variable results.

The MS stress model is a cost-effective and simple tool that supports the understanding of cognitive disorders, particularly those caused by early childhood stress. It can induce various cognitive, memory, and neuropsychological disorders, such as Alzheimer's disease, Parkinson's disease, dementia, anxiety, and depression. The model analyzes protein, genetic, and molecular factors to understand the pathological outcomes of early-life adversities. Future studies should use the MS stress model to understand the alterations caused in certain brain parameters to identify phenotypes and biomarkers. Utilizing the MS stress model in conjunction with prophylactic, diagnostic, and therapeutic approaches can lead to the discovery of potential therapeutic agents for a variety of neurodegenerative and neuropsychological disorders.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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