Review

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Low-Dose Radiation Therapy for Neurological Disorders: A Double-Edged Sword

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Radiation therapy targeting the central nervous system is widely utilized for the management of various brain tumors, significantly prolonging patient survival. Presently, investigations are assessing both clinical and preclinical applications of low-dose radiation (LDR) for the treatment of neuropathological conditions beyond tumor therapy. Special focus is given to refractory neurodegenerative diseases linked to neuroinflammation, such as Alzheimer's and Parkinson's diseases, where LDR has shown promising results. This comprehensive review examines the existing experimental data regarding the utilization of LDR in neurological disorders. It covers potential advantages in reducing neurodegenerative alterations and inflammation, as well as possible adverse effects, including neurological impairments. The review underscores the importance of the exposure protocol and the age at which LDR is administered in the context of the nervous system's pathological and physiological states, as these elements are crucial in determining LDR's therapeutic and toxic outcomes. The article concludes with a discussion on the future directions and challenges in optimizing LDR use, aiming to reduce toxicity while effectively managing neurological disorders.

Keywords: brain; low-dose radiation; neurological disorder; toxicity; therapeutic potential; neuroinflammation

Introduction

Radiation therapy is a pivotal treatment modality for various cancers, functioning mainly by inhibiting tumor cell growth and promoting their demise through reactive oxygen species (ROS) and DNA damage induction [1–3]. Despite its benefits, the use of ionizing radiation has been linked with diverse health effects over the past century [4]. Factors such as dosage, dose rate, and exposure duration significantly influence the lasting impacts of radiation [5]. Beyond direct exposure encountered by healthcare workers, both natural and artificial radiation sources are increasingly common [6]. With the expanding use and availability of radiation in medicine, it is crucial to reassess the literature on the biological effects of radiation on different human tissues and organs, especially the nervous system. Remarkably, over 50 percent of patients surviving six months or more after radiation therapy report cognitive difficulties [7]. High-dose irradiation can lead to impaired brain function or apoptosis in both mature and differentiating cells newly integrating into the hippocampal network, resulting in long-term functional deficits [8]. Despite the extensive documentation of neurobiological effects of high-dose radiation exposure [9–12], implications of low-dose exposure remain highly debated [13,14]. Lower doses may, paradoxically, provide beneficial effects, potentially triggering reparative mechanisms in central nervous system (CNS) pathologies [15,16], possibly via activating protective mechanisms, such as inducing antioxidant activity to counteract lipid peroxides [17]. Nonetheless, radiation exposure has been associated with developing neurological disorders [18,19], accelerating brain aging, and the progression of age-related neurological conditions [20,21]. This underscores a significant correlation between irradiation and the pathology of neurological diseases.

The term "neurodegenerative disease" encompasses a vast range of disorders characterized by various clinical and pathological features [22]. Their majority are marked by the accumulation of misfolded proteins, forming insoluble aggregates or inclusions within the CNS. This is often accompanied by a progressive neuron loss in the affected areas. Neurodegenerative diseases exhibit alterations in functional, molecular, and synaptic plasticity within the CNS, according to previous studies [22–25]. Unfortunately, pre-

cise treatments for nearly all neurodegenerative diseases are currently unavailable. The existing therapeutic strategies primarily aim at modifying disease progression to provide symptomatic relief [26]. These therapeutic interventions encompass a spectrum of approaches, including both pharmacological and non-pharmacological methods. The pursuit of effective treatments for neurodegenerative diseases poses a significant challenge, and current efforts are aimed at enhancing our understanding of the underlying mechanisms to develop more targeted and impactful interventions.

Low-dose radiation (LDR) protocols have shown potential in inducing and reversing these changes in several animal models of neurodegenerative diseases, including Alzheimer's disease (AD) [27,28] and Parkinson's disease (PD) [29,30]. Nevertheless, existing literature on LDR and its brain effects remain controversial. A thorough understanding of this relationship could be crucial for future applications of LDR in effectively mitigating neurological deficits without inducing toxicity. Therefore, this review focuses on the non-cancer effects of LDR exposure and the subsequent cellular responses in the CNS. Current research is exploring the molecular mechanisms underlying both the therapeutic and possible deleterious effects of LDR. Recently, LDR has gained attention as a potential therapeutic strategy for neurodegenerative diseases [26,31,32]. This review will critically examine the literature on the impact of LDR on the CNS, particularly addressing the ongoing uncertainties about the differing therapeutic and potentially harmful responses to LDR.

Retrieval Strategy

LDR generally includes doses ranging from approximately 0 mSv to 100 mSv (100 mGy) [31]. However, it is noteworthy that some studies classify doses up to 2 Gy within the low-dose category [33,34]. Defining LDR may pose challenges since both total dose and dose rates are considered. For the purposes of this review and to ensure uniformity and comparability, doses of 2 Gy or lower are defined as low-dose radiation therapy, aligning with doses employed in prior clinical pilot studies for AD treatment.

A comprehensive search for pertinent articles was undertaken using computer-based online databases, such as Google Scholar, PubMed, Web of Science, and Scopus between March 14, 2023 and October 1, 2023. This search was particularly focused on literature published in the past ten years. To achieve both precision and breadth in our search, we utilized a blend of text terms and Medical Subject Headings (MeSH). These encompassed terms like "neurological disorders", "neurodegenerative diseases", "neuroprotection", "brain", "neurotoxicity", "therapeutic effect", and "low dose irradiation" or "LDR" or "radiation therapy". The initial screening of the obtained results was based on titles and abstracts, focusing exclusively on studies that explored therapeutic or toxic effects on the nervous system due to LDR exposure. Additionally, only studies published in English were considered for inclusion.

Therapeutic Potential of LDR in Neurological Disorders

Neurodegenerative diseases pose a substantial global health challenge, encompassing disorders such as AD and PD [22]. Although the exact causes of these diseases remain elusive, they are thought to arise from a complex interplay of genetic factors and environmental influences, with aging as a key contributor. Ionizing radiation, a common tool in medical diagnostics and treatment, has gained attention as a potential therapeutic strategy for neurodegenerative disorders [35]. In particular, LDR presents unique advantages over conventional approaches such as brain exercises. LDR can globally stimulate adaptive protection mechanisms across the entire brain, in contrast to brain exercises, which may primarily enhance defenses in regions experiencing increased neuronal activity due to the exercises [36]. Consequently, several studies have highlighted LDR as a promising therapeutic approach for neurodegenerative conditions, offering a contrast to traditional methods [31,37,38]. While high-dose radiation is frequently employed in treating brain tumors and other organ-specific diseases, low-dose radiation is recognized for its array of beneficial effects in neurodegenerative disorders.

Therapeutic Effects of LDR in AD

The therapeutic potential of LDR in AD is supported by various evidence. Table 1 (Ref. [28,30,35,37–55]) presents a detailed summary of research on the therapeutic effects of LDR on different neurological disorders in both clinical and preclinical settings. The initial case report, which described significant improvements in an advanced AD patient receiving hospice care after undergoing five brain computed tomography (CT) scans (each approximately 40 mGy) over a period of three months in 2016, was a critical observation [39]. Following this, additional CT scans were carried out at the family's request, with 2018 follow-up results showing continued improvements in swallowing function and mood [40]. Another patient with early-stage AD who underwent LDR therapy reported temporary memory improvements [38]. However, due to concerns about the health effects of radiation, the LDR treatment was stopped after six CT scans, leading to disease progression in these patients. These findings led to the initiation of a clinical trial for LDR treatment in four AD patients, where three out of four patients showed cognitive improvements within a day of LDR exposure [37]. Additionally, two ongoing clinical trials are investigating different LDR treatment protocols: one with 2 Gy $\times$ 5 fractions in five patients [41] and another with 0.6 Gy $\times$ 5 fractions in five patients [42]. Interim reports from these trials indicate a

Table 1. Summary of the literature suggesting therapeutic potential of LDR in neurological disorders.

	Subject	Irradiation protocol	Additional treatment	End point after LDR	Therapeutic effect	Reference
Clinical	Advanced AD patient (n = 1)	5 CT scans for 3 months, 40 mGy/each treatment	-	-	- Restored impaired conversation, reading, and sense of humor	[37,39,40]
	Early-stage AD patient (n = 1)	6 CT scans, 46–50 mGy/each treatment			- Temporal improvement in impaired conversation, reading, and sense of humor	[38]
	AD patients (n = 4)	Three consecutive CT scans (40–89 mGy/each treatment, 2 weeks interval)	-	-	- Three patients showed cognition and behavior improvement within a day post-treatment	[37,38]
	Mild to moderate AD patient (n = 5)	Whole brain RT, 0.6 Gy × 5 over 1 week		Ongoing	- 1 of 5 patients experienced temporary improvement in language, memory, and frontal executive functions - Temporal nausea and mild hair loss reported	[42]
	AD patients (n = 5)	Whole brain RT, 2 Gy × 5 over 1 week		6 months after	- 3 of 5 patients demonstrated improvement in cognitive skills and imaging findings - No safety issues encountered	[41]
Preclinical	3×Tg-AD Mice	X-ray, 5 × 2 Gy	-	8 weeks post-IR	- Reduced Aβ plaque and tau expression	[28]
	12-month-old 3×Tg-AD	X-ray, 10 Gy in 5 daily fractions of 2 Gy	-	8 weeks post-IR	- Reduced Aβ42 aggregated forms in the hippocampus - Did not affect tauopathy or cognitive performance - A trend of reduced neuroinflammation	[44]
	TgF344-AD rats (presymptomatic)	X-ray, 10 Gy delivered in 5 daily fractions of 2 Gy	-	1 month post-IR	- Reduced 18-kDa TSPO-mediated neuroinflammation - Reduced all soluble and aggregated amyloid forms - Improved sAPPα levels showing a higher activation of the non-amyloidogenic pathway	[55]
	TgF344-AD rat	X-ray, 5 fractions of 2 Gy delivered either daily or weekly	-	4 months post-IR	- Daily treatment improved memory performance in the Y-maze - Weekly treatment increased the microglial reactivity in the hippocampus - No effect of either regimen on amyloid pathology	[45]

Table 1. Continued.

Subject	Irradiation protocol	Additional treatment	End point after LDR	Therapeutic effect	Reference
5×FAD mice	γ-ray , 0.038 mGy/h and 0.113 mGy/h for 112 days; cumulative dose of 0.1 and 0.3 Gy	-	At the end of 112 days	- No change in memory and locomotor function - No effect on the levels of APP, gliosis or inflammatory cytokines - Downregulated levels of IFN-γ	[35]
5×FAD mice	X-ray, 2 Gy per fraction for 5 times	-	8 weeks post-IR	- Reduced Aβ deposition - Improved cognitive deficits	[48]
5×FAD mice	X-ray, 9 Gy (1.8 Gy per fraction for 5 days)	-	4 days post-IR	- Short-term exposure did not affect Aβ accumulation in the brain - Significantly ameliorated synaptic degeneration, neuronal loss, and neuroinflammation	[46]
SH-SY5Y cells treated with Aβ1–42 (2 μM)	X-ray, single irradiation (1 Gy)	-	-	- Neuroprotective	[46]
5×FAD mice	X-ray, 5 × 0.6 Gy or 5 × 2 Gy	-	2–5 weeks post-IR	- Reduced levels of pro-inflammatory cytokines, microgliosis, amyloid plaque - Improved cognitive function	[47]
Human amyloid-β42 (Aβ42)-expressing *Drosophila* (0–6 h) embryos	γ-ray, 0.05 Gy	-	-	- Suppressed AD-like phenotypes - Did not alter the decreased survival rates and longevity of Aβ42-expressing flies - Suppressed Aβ42-induced cell death through regulation of the AKT and p38 MAPK signaling pathways	[43]
APP/PSEN1 Tg and WT mice	Protons, 150 MeV; 0.1–1.0 Gy (whole body)	-	3 and 6 months (Behavioral tests) and 6 and 9 months (Electrophysiology) post-IR	- Did not affect their behavioral performance - Reduced the amplitude of population spikes and inhibited paired-pulse facilitation in CA1 neurons - Increased excitability and synaptic efficacy - Increased Aβ deposition in the cortex of Tg mice without affecting cytokine levels - Increased synaptophysin expression in WT mice but not in Tg mice	[50]

Table 1. Continued.

Subject	Irradiation protocol	Additional treatment	End point after LDR	Therapeutic effect	Reference
B6.Cg-Tg (APPswePSEN1dE9)85Dbo/J AD-prone mice	X-ray, 1 Gy × 10, 2 Gy × 5, or 2 Gy × 10	-	24 h, 2, 4, or 8 weeks post-IR	- Reduced the number and size of Aβ plaques - Increased microglia at 4 weeks post-irradiation - Improved cognitive function	[49]
Male Wistar rats with intraperitoneal injection of reserpine	γ-ray, 0.5 Gy/s	*Ginkgo biloba* extract (EGb761®)	2 days post-IR	- Ameliorated oxidative stress, mitochondrial dysfunction, and apoptosis	[30]
Spinal cord injury in beagle dogs	X-ray, Once a day for 14 days (2 Gy per dose, 28 Gy)	-	1, 3, 7, 14, 30 and 60 post-injury	- Reduced astrocyte and microglia activation/proliferation - Attenuated CSPGs and IL-1β expression - Promoted and provided a pathway for long-distance axon regeneration beyond the lesion - Induced re-innervation of axonal targets - Restored locomotor function	[51]
Dexamethasone-induce diabetes in male albino rats	γ-ray, 0.1, 0.25, and 0.5 Gy	-	26 h after dexamethasone injection	- Ameliorated hyperglycemia and subsequently inhibited oxidative stress and apoptosis in brains - Increased the survival rate of diabetic animals	[52]
C57BL/6J mice	γ-ray, 0.063, 0.125, and 0.5 Gy		4, 12, 18 months post-IR	- Long-term and late-onset protective effects on brain and behavior	[53]
B6C3F1 mice	γ-ray, 0.063 Gy		24 months post-IR	- Induction of CREB pathway following LDR exposure with 0.063 Gy - Anti-inflammatory effects on hippocampus with reduced number of activated microglia	[54]
Human amyloid-β42 (Aβ42)-expressing Drosophila (0–6 h) embryos	γ-ray, 0.05 Gy	-	-	- Suppressed AD-like phenotypes - Did not alter the decreased survival rates or longevity of Aβ42-expressing flies - Suppressed Aβ42-induced cell death through regulation of the AKT and p38 MAPK signaling pathways	[43]

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid β; AKT, Ak strain transforming; APP, amyloid precursor protein; CA1, Cornu Ammnois 1; CSPG, chondroitin sulfate proteoglycan; CT, computed tomography; IFN, interferon; IL, interleukin; IR, irradiation; LDR, low-dose radiation; MAPK, mitogen-activated protein kinases; RT, radiation therapy; Tg, transgenic; TSPO, translocator protein; WT, wild-type; CREB, cAMP Response Element-Binding Protein; FAD, familial AD.

Radiation units: 1 mGy = 0.001 Gy, 1 cGy = 0.1 Gy.

modest improvement or stabilization of symptoms. Despite the small sample size, these studies in AD patients demonstrate temporary improvements and support the potential of LDR as a novel therapeutic approach for AD.

In animal models, LDR has shown promise in mitigating AD-like symptoms. For example, Hwang *et al.* [43] found that LDR effectively reduced AD-like symptoms in *Drosophila* embryos expressing human amyloid-β42 (Aβ42). Additionally, LDR has been observed to decrease Aβ and tau levels in 3×transgenic (Tg) mouse models for AD [28,44]. In a TgF344-AD rat model, LDR was noted to reduce translocator protein-mediated neuroinflammation, improve memory performance, and diminish amyloid accumulation [44,45]. LDR also showed a neuroprotective impact in preventing neuronal loss and synaptic degeneration in the hippocampus of 5×familial AD (FAD) mice [46–48], as well as in SH-SY5Y neuroblastoma cells exposed to Aβ [46]. Conversely, a recent study using the same animal model (5×FAD mice) indicated that chronic exposure to LDR did not significantly impact memory, locomotion, or amyloid precursor protein (APP) expression, except for a reduction in interferon-γ signaling [35]. In APP/PSEN1 Tg mice, LDR led to a decrease in the number and size of Aβ plaques and an improvement in cognitive function [49]. Yet, another study using the same model reported that LDR increased Aβ deposition in the cortex without affecting cytokine levels and behavioral performance [50].

Therapeutic Effects of LDR in PD

LDR has been explored as a potential therapeutic option for PD in animal models. In PD animal models, LDR exhibited significant neuroprotective effects. It alleviated oxidative stress, mitigated mitochondrial dysfunction, and reduced apoptosis in the brains of PD rats induced by reserpine [30]. Beyond neurodegenerative diseases, LDR has shown potential in addressing different neurological conditions across various animal models. Its experimental use extends to other neurological disorders. For instance, in beagle dogs with spinal cord injury, LDR promoted axonal regeneration and enhanced locomotion [51]. Additionally, LDR exhibited anti-apoptotic and antioxidant effects in brain injury induced by diabetes in rats [52].

Mechanisms Involved in the Therapeutic Effects of LDR in Neurological Disorders

It is essential to highlight that the majority of research investigating the therapeutic potential of LDR primarily focuses on disease models for neurodegenerative conditions. This focus poses a challenge for making direct comparisons with effects on a healthy brain. A previous study revealed delayed yet beneficial effects on exploratory behavior and sensorimotor abilities in C57BL/6 mice, suggesting a positive impact of LDR on behavior [53]. This group has also shown that whole-body exposure to LDR (63 mGy) leads to the activation of cAMP Response Element-Binding Protein (CREB) signaling and a reduction in neuroinflammation, indicating a potential role for LDR in neuroprotection [54]. Furthermore, LDR has shown promising benefits in well-known neurodegenerative disease models, such as AD and PD. In a recent comprehensive review, Jebelli *et al.* [31] focused on the therapeutic effects of LDR, particularly in the context of AD. Therefore, additional research is required to develop standardized protocols and to fully understand the therapeutic effects of LDR on neurological disorders.

The studies listed in Table 1 employ a variety of methodologies and concentrate on different aspects of LDR therapy. Data from earlier studies exhibit a wide range of variability concerning dose, duration of exposure, selection of animal models, and the timing of assessments. Despite variations in irradiation protocols across different studies, we have endeavored to identify potential patterns in therapeutic irradiation doses across preclinical experiments. Most studies indicate that a fractional irradiation of 2 Gy administered in 5 doses, reaching a total dose of 10 Gy of X-ray irradiation, demonstrates therapeutic effects in various animal models. Furthermore, this protocol has been validated for its efficacy in cases where either partial or complete brain irradiation was administered. However, it is crucial to note that these findings may not directly translate to human cases. Generating a definitive conclusion on the optimal irradiation dose for therapeutic effects in humans remains challenging due to the limited available literature. Importantly, one research group, known for providing early insights into the immediate effects of LDR on the brain, found that LDR activates protective mechanisms in aged rat brains by decreasing lipid peroxides and increasing antioxidant activity [17]. Conversely, Lowe *et al.* [56] reported that molecular responses in the mouse brain a few hours after LDR exposure include the downregulation of neural pathways linked to cognitive dysfunctions, which are also downregulated in normal human aging and AD. However, it is important to acknowledge that the therapeutic effects of LDR on neurodegenerative diseases are mainly observed after chronic or long-term exposure following irradiation.

Overall, the existing evidence derived from animal studies indicates that LDR is unlikely to cause harmful changes in cognitive abilities, cellular processes, DNA, and gene expression [31,52]. Additionally, research utilizing mouse models has shown that LDR exposure to the brain may enhance the proliferation of neural stem cells, thereby facilitating neurogenesis in the hippocampus through the Wnt/β-catenin signaling pathway [57]. Consequently, the potential therapeutic applications of LDR in these models may primarily involve enhancing stem cell proliferation, neurogenesis, and possibly mitigating oxidative stress [58]. In addition to these processes, LDR has been observed to prevent cell death induced by human Aβ42, by modulating various signaling pathways, including the Ak strain transforming (AKT) and p38 mitogen-activated protein kinase

pathways [43]. Nevertheless, the exact mechanisms underlying the therapeutic effects of LDR are not fully elucidated, emphasizing the need for additional research.

Neurobiological Toxicity of LDR

Toxicity of LDR in Early Developmental Exposure

The neurobiological impact of LDR has been thoroughly investigated, primarily using experimental animals, as detailed in Table 2 (Ref. [33,34,53,59–83]). Preclinical studies have identified various adverse effects on the nervous system, especially when exposure occurs during early developmental stages. Notably, neonatal mice exposed to LDR around postnatal day (PND) 10 exhibited significant short-term and long-term brain function disruptions. For example, a study demonstrated that γ-irradiation on PND 3 or 10 led to altered adult spontaneous behavior and impaired habituation, whereas irradiation on PND 19 did not affect these behaviors in Naval Medical Research Institute (NMRI) mice [59]. Mice exposed to γ-rays at PND 10 exhibited reduced mitochondrial function and synaptic plasticity at 24 hours, 4–5 weeks, and even 6 months post-exposure [60,84]. Similarly, exposing PND 10–12 mice to X-rays resulted in locomotion impairments and hippocampus-dependent behavioral changes, along with histological and volume alterations in the neocortex [61]. Moreover, X-irradiation on embryonic day (ED) 11 in mice led to decreased phosphorylation of cAMP response element-binding protein in the hippocampus and cortex, and increased expression of postsynaptic density protein 95 [85]. NMRI mice exposed to γ-rays at PND 10 showed cognitive decline at 2–4 months, alongside elevated tau levels in the cerebral cortex [62]. Additionally, γ-irradiation of PND 10 mice acutely impaired RhoGTPase-Rac Family Small GTPase 1 (Rac1) in the brains of NMRI mice and in hippocampal HT23 cells *in vitro* [63]. NMRI mice exposed to γ-rays at PND 10–12 exhibited disrupted habituation behavior at 2 months [74]. In mice with varying DNA repair capabilities due to genetic modifications, exposure to LDR at different fractions of 100 mGy on PND 11 or PND 56 led to reduced hippocampal neurogenesis and increased numbers of persistent 53BP1-foci in juvenile mice 72 hours after 5x fractionated LDR exposure [75].

Long-Term Toxicity of LDR

Beyond the early developmental stages, exposure to radiation in adulthood has also been linked to changes in brain function. Mice subjected to proton radiation showed deficits in learning and memory at 3 and 6 months after exposure [76]. Various radiation protocols in mice resulted in alterations in hippocampus-dependent behavior and DNA damage at different intervals [77–80]. Additionally, mice subjected to radiation for 21 days experienced increased lipid peroxidation in the hippocampus and cortex at 7 days and 9 months post-exposure [81]. Thy1-EGFP MJrs/J Tg mice exposed to protons exhibited a dose-dependent decrease in structural plasticity in the hippocampus [82]. Fractionated LDR induced sustained inflammatory responses, marked by heightened activity of microglia and astrocytes, especially in the juvenile hippocampus in the initial months after LDR [83]. SHK mice showed emotional and cognitive impairments, along with neuronal damage, 2 months after LDR exposure [64]. Mice with a mutation in the excision repair cross-complementing rodent repair deficiency, complementation group 2 (ERCC2) DNA repair gene and exposed to X-ray exhibited behavioral and molecular changes at various intervals, including 4, 12, and 18 months post-exposure [53]. Notably, the impact of radiation was dose-dependent, with higher doses leading to early and persistent adverse effects, while lower doses showed some protective effects on sensorimotor functions and exploratory behavior [53]. Furthermore, mice exhibited a decrease in the survival of hippocampal neural progenitor cells and reduced neurogenesis following radiation. In contrast, CC motif chemokine receptor 2 (CCR2) knockout mice showed resilience to radiation-induced decreases in these areas [34]. In Tg2576 and PS19 Tg mice, LDR triggered an early transcriptional response of AD-related genes in the hippocampus, yet without leading to AD-like pathologies or memory deficits [86]. Even in wild-type mice subjected to LDR, depressive-like behaviors, reduced hippocampal neurogenesis, and persistent neuroinflammation were observed 30 and 90 days post-exposure [33,65].

Previous research involving rodents has demonstrated that low-dose exposure to charged particles below 1 Gy can lead to behavioral impairments associated with disruptions in brain regions, especially the hippocampus [64,66–69,76,78,79,82]. Specifically, proton irradiation at doses of 0.1 and 1 Gy [82] results in dose-dependent reductions in dendritic complexity and spines in the dentate gyrus. Moreover, exposure to 0.5 Gy of protons adversely affects reversal learning and alters electrophysiology [76], whereas ^{16}O-particle irradiation at a dose of 0.05 Gy causes impaired novel object recognition and a decrease in hippocampal spine density [66]. Simultaneous exposure to ^{1}H (0.5 Gy) and ^{16}O (0.1 Gy) particles leads to cognitive impairment and reduced dendrite length three months after irradiation [67]. Other observations include spatial memory deficits following ^{48}Ti-particle irradiation (5 cGy) [68], impaired attentional set-shifting due to ^{28}Si-particle exposure (5 cGy) [69], and hippocampal anomalies, disrupted fear memory, anxiety, and diminished new neuron survival in males as a result of ^{28}Si-particle irradiation (0.2 and 1 Gy) [79]. Additionally, accelerated carbon ion exposure (0.7 Gy) induces anxiety, impaired memory retention, and a reduction in dorsal hippocampal cells two months post-irradiation [64]. Considering that ion beams in radiotherapy possess an increased relative biological effectiveness (RBE), which is influenced by ion type, energy level, and

Table 2. Summary of literature supporting the neurotoxic effects of low-dose irradiation.

Subject	Irradiation protocol	Additional treatments	End point	Effect on the brain	Reference
Male NMRI mice (PND 3, 10, and 19)	γ-ray, 500 mGy	-	2 months of age	- Altered adult spontaneous behavior - Impaired habituation capacity - Irradiation on PND 19 did not have any impact	[59]
Female C57BL/6J mice (PND 10)	γ-ray, 0.1 or 0.5 Gy	-	24 h post-IR	- Reduced mitochondrial function - Enhanced number of dendritic spines and neurite out-growth - Elevated long-term potentiation and increased phos-phorylated CREB - Increased expression of several neural miRNAs asso-ciated with synaptic plasticity	[60]
Female C57BL/6J mice (PND 11)	γ-ray, 0.1, 0.5, or 2.0 Gy	-	4–5 weeks or 6 months post-IR	- Impaired oxidative phosphorylation in synaptic mito-chondria - Reduced mitochondrial respiration capacity (4 weeks)	[60]
C57BL/6J mice (ED 10, 11 or 12)	X-ray, 0.1, 0.2, 0.5, or 1.0 Gy	-	12 weeks of age	- Impaired locomotor behavior and hippocampus-dependent spatial learning and memory - Increased p53-mediated apoptotic response - Reduced total brain volume, cortical thickness, and ventricle size	[61]
C57Bl/6J offspring (ED 11)	X-ray, 0.1, 0.5, and 1.0 Gy	-	6 months post-IR	- Reduction in p-CREB level - Enhanced expression of PSD95	[60]
NMRI mice (PND 10)	γ-ray, 500 mGy	-	2 and 4 months of age	- Displayed a modified habituation - Reduced cognitive function - Increased levels of tau protein	[62]
Male NMRI mice/PND 10	γ-ray, 1 Gy	-	24 h post-IR	- Impaired Rho GTPase/Rac1	[63]
Male NMRI mice	γ-ray, 200 mGy PND 10, 10–11, 10–12, or 10–13	Nicotine (66 µg/kg) twice daily	2 months of age	- Disrupted behavior and habituation - Altered susceptibility of cholinergic system	[74]
C57BL/6 mice	γ-ray, 50–200 mGy at PND10	Ketamine	2, 4, and 5 months of age	- Co-exposed animals showed lack of habituation in spontaneous behavior - Impaired learning and memory - Elevated levels of tau protein	[78]
C57BL/6 mice	X-ray, 0.1 Gy	-	2 days post-IR	- Increased level of DNA damage	[76,80]
C57BL/6 mice	γ-ray, 2 Gy	-	30 days post-IR	- Depression-like symptoms - Reduced hippocampal neurogenesis	[33]

Table 2. Continued.

Subject	Irradiation protocol	Additional treatments	End point	Effect on the brain	Reference
C57BL/6 mice	γ-ray, 1 and 10 Gy	-	30 and 90 days post-IR	- Depression-like symptoms - Reduced hippocampal neurogenesis - Hippocampal neuroinflammation	[65]
Male CCR2 KO mice	γ-ray, 0.1, 2 Gy, and 0.1 + 2 Gy	-	30 days post-IR	- CCR2 KO protects against LDR-induced neuroinflammation and reduced neurogenesis	[34]
C57BL/6 mice	X-ray, 0.1 Gy	-	2 days post-IR	- Increased level of DNA damage	[80]
Tg2576 mice and PS19 mice	X-ray, 5 or 10 cGy	-	4 h, 62, and 114 weeks post-IR	- Induced early transcriptional response of several AD-related genes in hippocampi without late AD-like pathogenesis and memory impairment	[65]
Female C57BL/6J mice	X-ray, 100 mGy	-	5 h post-IR	- Downregulated *APBB*1 and *LRP1* gene expression - No change in memory function - No induction of amyloid fibrillogenesis or changes in APP, Aβ, tau, or p-tau expression	[72]
C57BL/6 and ATM-/- and DNA-PKcs-/- mice	X-ray, 5×, 10×, 15× and 20× fractions of 100 mGy		72 h post-IR	- Increased DNA damage accumulation - Declined hippocampal neurogenesis	[75]
C57BL/6 mice	γ-ray, 0.04 Gy for 21 days	-	7 days or 9 months post-IR	- Elevated lipid peroxidation in the cortex and hippocampus - Decrease in SOD expression	[81]
Adult and juvenile C57BL/6NCrl mice	X-ray, 20 fractions of 0.1 Gy daily	-	72 h and 1, 3, and 6 months post-IR	- Induced long-lasting inflammatory responses with local increases of activated microglia and reactive astrocytes (most pronounced in the juvenile hippocampus 1 month post-IR)	[83]
ERCC2 point mutation mice	X-ray, 0.063, 0.125, or 0.5 Gy	-	4, 12, and 18 months post-IR	- High-dose IR had early-onset adverse effects 4 months post-IR on sensorimotor recruitment and late-onset negative locomotor effects 12 and 18 months post-IR - Low-dose IR produced no early effects, but subtle late-onset (18 months) protective effects on sensorimotor recruitment and exploratory behavior	[53]
C57BL/6 mice	Cosmic IR, 5 or 30 cGy	-	6, 15, or 52 weeks post-IR	- Cognitive impairment	[77]
Tg(Thy1-EGFP)MJrs/J mice	Whole body proton IR, 0.1 and 1 Gy	-	10 and 30 days post-IR	- Reduced dose-dependent dendritic complexity, reductions in the number and density of dendritic spines in DGs	[82]

Table 2. Continued.

Subject	Irradiation protocol	Additional treatments	End point	Effect on the brain	Reference
Male C57Bl/6 mice	Proton, 0.5 Gy	-	3 and 6 months (Morris water maze and Barnes maze) and 9 months (Electrophysiology) post-IR	- Impaired reversal learning - Did not affect LTP but significantly increased fEPSP slopes	[73,76]
C57BL/6 mice	^{16}O-particle-IR, 0.05 Gy		275 days post-IR	- Impaired novel object recognition - Decreased in mushroom spine density in the hippocampus	[66]
C57BL/6 mice	^{1}H (0.5 Gy) and ^{16}O (0.1 Gy)-particle-IR		3 months post-IR	- Impaired cognitive performance - Reduced dendrite length and complexity	[67]
Wistar rats	^{48}Ti-particle-IR, 5 cGy		3 months post-IR	- Reduced spatial memory performance - Increased percentage of severe impairment	[68]
Wistar rats	^{28}Si-particle-IR, 5 cGy		3 months post-IR	- Impaired attentional set-shifting performance	[69]
C57BL/6 mice	^{28}Si-particle-IR, 0.2 and 1 Gy	-	24 h and 3 months post-IR	- Abnormalities in hippocampal function - Disrupted fear memory, induced anxiety-like behavior - Decreased new neuron survival in males	[65,79]
Male SHK1 mice	Accelerated carbon ions, 0.7 Gy	-	2 months post-IR	- Anxiety and shortage in hippocampal-dependent memory retention - Reduced number of cells in the dorsal hippocampus	[64]
Primary mouse embryonic neuronal stem cell types (Striata, Cortex, and Ventral mesencephalon ED14)	Proton IR 250 MeV, 0.5 and 1 Gy, silicon ions 260 MeV/u 0.2 and 0.5 Gy, and iron ions 1 GeV/u 0.2 and 0.5 Gy	-	24 h post-IR	- Changed markers of neural progenitor and stem cells in DNA binding/damage repair and cellular redox pathways	[70]
Cultured human neural progenitor cells	γ-ray, 31, 124, and 496 mGy	-	72 h post-IR	- Altered pathways involving INF signaling and cell junctions - Affected DNA repair and synthesis, apoptosis, metabolism, neural differentiation, and cell adhesion molecules	[71]
Hippocampal HT23 cells	γ-ray, 0.5, 1.0, and 4.1 Gy	-	4 and 24 h post-IR	- Affected signaling related to synaptic actin-remodeling - Reduced miR-132 and Rac2 levels	[63]

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid β; *APBB1*, amyloid beta precursor protein binding family B member 1; APP, amyloid precursor protein; CREB, cAMP Response Element-Binding Protein; CCR2, CC motif chemokine receptor 2; ED, embryonic day; ERCC2, excision repair cross-complementing rodent repair deficiency, complementation group 2; fEPSP, field excitatory postsynaptic potential; IR, irradiation; KO, knockout; LDR, low-dose radiation; LTP, long-term potentiation; *LRP1*, LDL receptor-related protein 1; NMRI, Naval Medical Research Institute; PND, postnatal day; PSD95, postsynaptic density 95; Rac1, Rac Family Small GTPase 1; Rac2, Rac Family Small GTPase 2; Tg, transgenic.
Radiation units: 1 mGy = 0.001 Gy, 1 cGy = 0.1 Gy.

biological characteristics, the RBE denotes the ratio of the dose of reference radiation (typically high-energy γ- or X-rays) to the dose of a test radiation type necessary for a comparable biological effect. Protective weighting factors are assigned based on RBE values, with values of 1 for X-rays and γ-rays, 2 for protons, 20 for alpha particles, heavy ions, and energy-dependent values for neutrons [87]. Therefore, even at low radiation doses, the variation in biological effects must be taken into account when evaluating the impact on the brain.

In vitro studies have consistently demonstrated neuronal damage following irradiation. For example, primary cortical neurons showed an increase in lactate dehydrogenase release and a proliferation of microglia 24 hours after irradiation [88]. Similarly, primary mouse embryonic neuronal stem cells from various brain regions exhibited changes in proteins that are typical markers of neural progenitor and stem cells within the same timeframe [70]. Cultured human neural progenitor cells revealed an upregulation of inflammatory pathways and DNA repair mechanisms 72 hours after irradiation [71]. However, Wang *et al*. [72] observed that LDR only caused a downregulation in the expression of amyloid beta precursor protein binding family B member 1 (*APBB1*) and LDL receptor-related protein 1 (*LRP1)* genes in mice 4 hours post-irradiation, without affecting memory function or altering the expression of pathological proteins such as APP, tau, and Aβ.

Mechanisms Involved in the LDR Toxicity in Neurological Disorders

The neurotoxic effects of irradiation have been extensively studied [89–91]. Both young and adult animals show similar patterns of behavioral dysfunction following radiation exposure. Notably, molecular, synaptic, and mitochondrial alterations are more evident in mice irradiated at younger ages. In these animals, the most susceptible period for irradiation damage aligns with embryoinic days (ED) 11 and 12, which is comparable to early gestational weeks 7 and 8 in humans [92]. This correlation is significant, considering this timeframe coincides with the initial formation of neurons in the cerebral cortex [93,94]. While various molecular mechanisms have been suggested to underlie the behavioral deficits observed in neonatal and adult mice exposed to radiation, these findings could be relevant for patients receiving radiation therapy. Radiation exposure induces immediate changes in dendritic spines and synapses, particularly in the cortical and hippocampal areas, driven by abnormal cytoskeletal signaling and processing, leading to neurocognitive effects [60,63,76]. Further research is needed to fully understand the pathways responsible for radiation-induced brain alterations.

The majority of these studies identify the neurotoxicity of LDR as primarily linked to exposure in the early postnatal period (Table 2). Mice exposed to LDR during this crucial developmental stage exhibit negative phenotypes and molecular changes as soon as 24 hours post-exposure, persisting for up to six months. The toxic effects, irrespective of the exact timing, predominantly involve impaired behavior, hindered neurogenesis, mitochondrial malfunction, and synaptic disturbances. However, some studies also highlight the potential harmful impact of LDR on the adult brain, marked by similar pathological manifestations [33,78]. Therefore, future research is vital to determine the critical exposure periods that cause cellular, molecular, and behavioral alterations in developing versus mature brains.

Prospects

While the majority of research has focused on the therapeutic potential of LDR for common neurodegenerative conditions, our understanding of its potential benefits in other neurological disorders, such as multiple sclerosis, traumatic brain injury, and ischemic stroke, remains limited. Most preclinical studies have utilized genetic models for neurodegenerative diseases, leaving the effects of LDR on toxin- or drug-induced models largely unexplored. Investigating the therapeutic potential of LDR for other neurological conditions beyond major neurodegenerative diseases is also important in upcoming research.

Studies examining LDR-induced neurotoxicity have revealed a trend where early life exposure leads to more pronounced neurotoxic effects in adulthood. However, this finding may not directly apply to humans, who are often exposed to varying levels of environmental radiation as adults. Therefore, investigating potential neurotoxic effects arising from LDR exposure during adulthood in future studies is imperative. Additionally, understanding the underlying mechanisms that drive both the therapeutic and toxic effects of LDR is crucial.

This review primarily focused on studies exploring the therapeutic effects of LDR on neurological disorders and its potential neurotoxic impacts on the CNS. However, the potential therapeutic and toxic effects of LDR on other body tissues should not be overlooked. Research into the effects of LDR on individual organs or inter-organ interactions offers an intriguing avenue for further exploration in future discussions and research endeavors.

Conclusions

A substantial body of literature supports both the therapeutic and potentially neurotoxic effects of LDR on the nervous system, encompassing normal physiological states and various neurological disorders. Essentially, LDR exerts a dual influence on nervous system health. Limited clinical studies in patients with AD have shown that low-dose repeated irradiation yields both temporary and sustained therapeutic effects. However, treatment discontinuation in some cases due to radiation-related concerns highlights the necessity of establishing a safety profile in conjunction with treatment efficacy. Importantly, even at very low doses, cu-

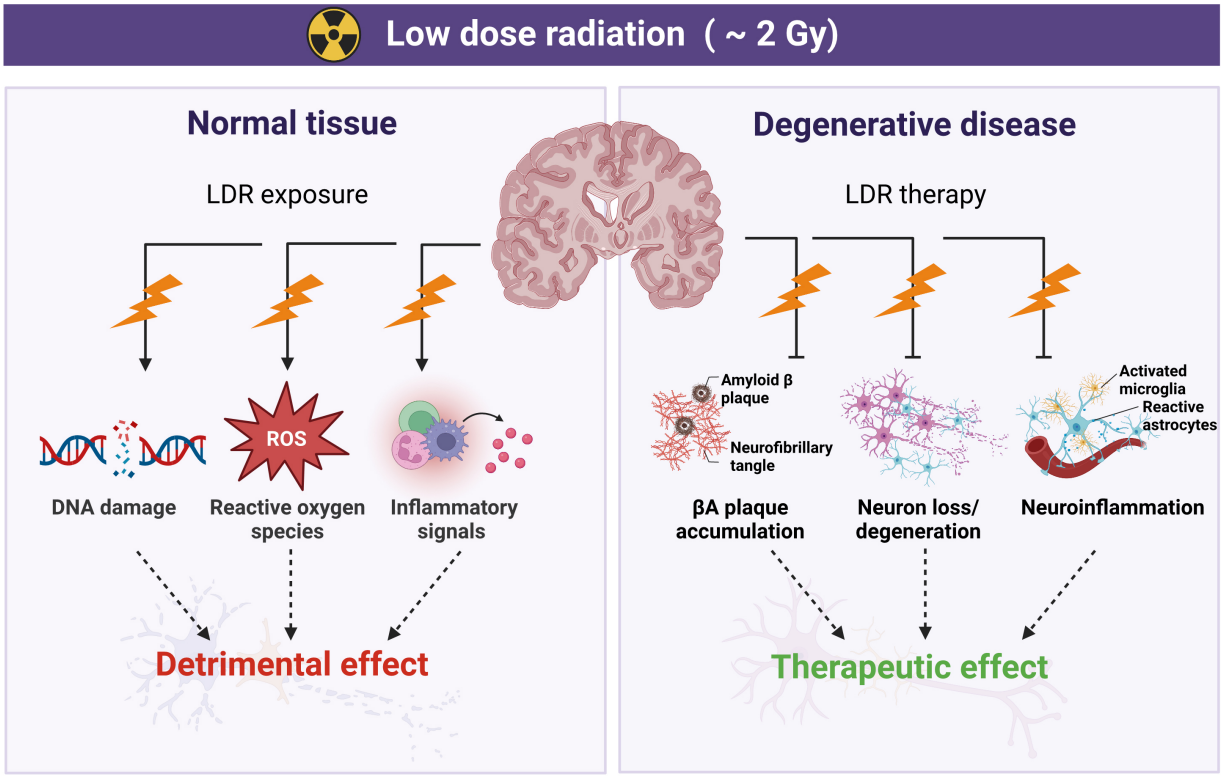

Fig. 1. Effects of LDR on the brain: A double-edged sword. This figure illustrates both the detrimental and beneficial effects of low-dose radiation on normal brain function and in conditions related to neurological disorders. βA, beta-amyloid; LDR, low-dose radiation; ROS, reactive oxygen species. Figure generated via BioRender.com.

mulative exposure or exposure to high-energy particles can increase side effects. The specific functional and molecular changes induced by LDR are increasingly being understood, underlining the urgent need for a comprehensive understanding of the complex mechanisms driving both its therapeutic potential and risks (Fig. 1). Such knowledge is vital for the careful and safe use of LDR in future clinical applications.

Moreover, refining protocols for LDR exposure as a potential therapeutic strategy for a range of neurological disorders, including neurodegenerative diseases, shows promise. Future research should focus more on exploring the mechanisms by which LDR influences neurophysiopathology, whether therapeutically or adversely. Efforts should also aim to optimize the LDR exposure protocol to achieve the best therapeutic outcomes for specific neurological conditions. By doing so, we can maximize the potential benefits of LDR while mitigating any associated risks.

Availability of Data and Materials

Not applicable.

Author Contributions

PDEWM, JSK, HJL, and CM conceptualized the research study. PDEWM, JSK, SK, YS, YSL, HJL, and CM were involved in data acquisition. Data analysis was carried out by PDEWM, JSK, HJL, and CM. The original draft was written by PDEWM, JSK, HJL, and CM, who also reviewed and edited the manuscript. HJL and CM provided supervision for the research study. All authors made significant editorial contributions to the manuscript and reviewed and approved its final version. Additionally, all authors have participated significantly in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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