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Review article

Postnatal irradiation-induced hippocampal neuropathology, cognitive impairment and aging

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Abstract

Irradiation of the brain in early human life may set abnormal developmental events into motion that last a lifetime, leading to a poor quality of life for affected individuals. While the effect of irradiation at different early developmental stages on the late human life has not been investigated systematically, animal experimental studies suggest that acute postnatal irradiation with $\geqslant$0.1 Gy may significantly reduce neurogenesis in the dentate gyrus and endotheliogenesis in cerebral vessels and induce cognitive impairment and aging. Fractionated irradiation also reduces neurogenesis. Furthermore, irradiation induces hippocampal neuronal loss in CA1 and CA3 areas, neuroinflammation and reduces gliogenesis. The hippocampal neurovascular niche and the total number of microvessels are also changed after radiation exposures. Each or combination of these pathological changes may cause cognitive impairment and aging. Interestingly, acute irradiation of aged brain with a certain amount of radiation has also been reported to induce brain hormesis or neurogenesis. At molecular levels, inflammatory cytokines, chemokines, neural growth factors, neurotransmitters, their receptors and signal transduction systems, reactive oxygen species are involved in radiation-induced adverse effect on brain development and functions. Further study at different omics levels after low dose/dose rate irradiation may not only unravel the mechanisms of radiation-induced adverse brain effect or hormesis, but also provide clues for detection or diagnosis of radiation exposure and for therapeutic approaches to effectively prevent radiation-induced cognitive impairment and aging. Investigation focusing on radiation-induced changes of critical brain development events may reveal many previously unknown adverse effects.

Keywords: Postnatal radiation; Brain pathology; Cognition; Molecular mechanisms

1. Introduction

Radiosensitivity of the brain is dependent on the age, sex, strains and species of animals and cell types. The developing brain is in general more radiosensitive than mature brain due to much more cell divisions in immature animals. In the first two years of age, the human brain is very sensitive to radiation due to rapid brain development (weight reaches to 90–95% adult brain) including synaptogenesis, myelination and changes of neurotransmitter and receptor systems [1,2]. For the mice, postnatal day 10 (P10) represents the developmental stage most sensitive to neurotoxic insults. Brain growth, gliogenesis, axonal and dendrite increase and oligodendrocyte maturation peak at this stage [2,3]. Therefore, information on the radiation effect on immature brain at different postnatal development stages and

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Table 1
High dose ionizing radiation–induced development changes of the hippocampus in immature rodents.

Animal strains	Radiation source	Age and dose	Endpoint: animal age or post irradiation time	Neuronal or glial reactions	References
Sprague–Dawley rats	X-rays	2 Gy at P0	6 h	Cell death (neurons, glial cells, immature cells) in the primary and secondary germinal zones, in the cortical layers of the olfactory bulb, layers II-III and VIb of the neocortex, piriform and entorhinal cortex, stratum oriens and pyramidale of the hippocampus, striatum, thalamus, amygdala, brainstem, internal granular layer of the cerebellum, and cerebral and cerebellar white matter	Ferrer et al. [7]
Wistar rats	γ-Rays (head)	6 Gy at P0 (taken as day of birth)	From P3 to P60	Reduction of dentate granule cells, CA1 pyramidal neurons and their thorny excrescences per neurons, mossy fibers in the hilus and the stratum lucidum	Gaiarsa et al. [8]
Sprague–Dawley rats	X-rays (SVZ or SGZ)	5, 10, 15 Gy at P0 for SVZ, 15 Gy from P0 to P30 for SGZ	P9, P16, P32, P62, P92	Reduction of proliferating cells in SVZ in a dose-dependent manner, down-regulation of neural stem/progenitor cell associated proteins	McGinn et al. [9]
Sprague–Dawley rats	X-rays	2 Gy at P1 or P15	3 to 48 h	At P1, the number of dying cells rapidly increased in the hippocampal complex with peak values 6 h after irradiation. Cell death was not induced by X-irradiation in rats aged 15 days	Ferrer et al. [10]
Wistar rats	X-rays (head)	2 Gy on P1, P2, P3, followed by 1.5 Gy on P5, P7, P9, P12, P15	From P23 to P135	A marked reduction in the number of the developing granular neurons in the dentate gyrus and a marked increase in the specific activity of acetylcholinesterase (AChE) and choline acetyltransferase (CAT)	Ben-Barak [11]
Rats [Crl: CD(SD)BR]	X-rays (head)	2 Gy on P1, 2, 1.5 Gy on P5,7,9, 12, 14 and 16, a total of 13 Gy	P133	Significant depletion of dentate granule cells, perseveration in spontaneous exploration of the arms of a T-maze, retarded acquisition of a passive avoidance task, and increased horizontal locomotion	Mickley et al. [12]
Purdue-Wistar rats	X-rays (head)	1.5–2 Gy at P2 with 2, 4, 6 or 8 doses. In 8× group, 2 Gy was delivered on P2, P3 followed by 1.5 Gy on P5,7,9, 11, 13 and 15. In 6×, 4×, or 2× group, 2 Gy, the last exposure on P11, P7, P3 respectively.	P30, P60, P90 and P120 respectively	The number of granule cells of the dentate gyrus was progressively and permanently reduced from control levels by the different dosage schedules, i.e., 2×, 59% reduction; 4×, 77%; 6×, 83%; 8×, 84%	Bayer & Altman [13]
Spraque-Dawley rats	X-rays	2 Gy on P2, P3, 1.5 Gy on P5,7,9,11, 13 and 15, a total of 13 Gy	P16-17, P60-65	Severe hippocampal granule cell hypoplasia and deficits in a memory-based discrimination	Diaz-Granados et al. [14]
C57 BL/6 mice	X-rays (head)	6 Gy at P9	36 h and P93	Decreased neurogenesis at 36 h and P93 after irradiation. Voluntary running rescued adult hippocampal neurogenesis after irradiation	Naylor et al. [22]
Wistar rat	X-rays (head)	6 Gy at P9	24 h or 63 days	A drastic reduction of neurogenesis at 1 day, of neurogenesis and radial glia-like stem cells in the dentate gyrus at 2 months after irradiation	Hellstrom et al. [23]
Wistar rat	X-rays (head)	6 Gy at P9	16 h	Microglia in the hippocampus responded less favorably to stem cell recovery, whereas those from the SVZ might be involved in stem cell maintenance, proliferation, and survival	Hellstrom et al. [24]
Wistar rats	X-rays (head)	8 Gy at P9, P21	6 h, 7 days	Activated multiple inflammatory mechanisms in the acute phase 6 h after irradiation. Down-regulation of genes related to neurogenesis and cell cycle, up-regulation of glial fibrillary acidic protein (GFAP), hypertrophy, but not hyperplasia of astrocytes 7 days after irradiation. Irradiation (8 Gy) also induced loss of microglia in the young brain (P9 and P21)	Kalm et al. [25,26]
C57BL/6 mice	X-rays (head)	6 Gy at P10	P70	Irradiation reduced neurogenesis in the granule cell layer of the dentate gyrus	Barlind et al. [27]