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Effects of ionizing radiation on the mammalian brain

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ABSTRACT

Epidemiological studies on the atomic-bomb survivors, cancer survivors and occupational cohorts provide strong evidence for multifaceted damage to brain after ionizing radiation. Radiation-induced late effects may manifest as brain tumors or cognitive impairment. Decreased neurogenesis and differentiation, alteration in neural structure and synaptic plasticity as well as increased oxidative stress and inflammation are suggested to contribute to adverse effects in the brain. In addition to neural stems cells, several brain-specific mature cell types including endothelial and glial cells are negatively affected by ionizing radiation. Radiation-induced enhancement of endothelial cell apoptosis results in disruption of the vascular system and the blood brain barrier. Activated microglia create inflammatory environment that negatively affects neuronal structures and results in decreased synaptic plasticity. Although the molecular mechanisms involved in radiation-induced brain injury remain elusive, first strategies for prevention and amelioration are being developed. Drug-based prevention and treatment focus mainly on the inhibition of oxidative stress and inflammation. Cell replacement therapy holds great promise as first animal studies using transplantation of neural stem cells to irradiated brain have been successful in restoring memory and cognition deficits. This review summarizes the epidemiological and biological data on radiation-induced brain damage and describes prevention and therapy methods to avoid and ameliorate these adverse effects, respectively.

1. Introduction

Human populations are increasingly being exposed to ionizing irradiation (IR) from various sources. We all encounter daily natural radiation including cosmic rays, environmental radionuclides or radon decay products typically providing low-dose low-dose-rate exposure. IR can also originate from man-made sources in the context of nuclear accidents, nuclear weapons testing and unplanned discharges of radioactive waste [1]. Some individuals are additionally receiving occupational exposure related to nuclear technologies, airline travel or even space exploration. The explosive growth in the use of medical diagnostics and therapeutic radiology has led to a marked increase in the number of individuals receiving repeated exposure to IR [2].

Radiation therapy has been commonly used as the standard treatment for nearly all tumor diseases [3]. Especially in the case of brain tumors, the application has been limited by the risk of radiation-induced damage to the normal tissue and subsequent devastating functional deficits. Improvements in medical applications of radiation therapy have enabled a more efficient diagnosis and treatment of brain cancer patients, resulting in increased survival rates and longer post-cancer lifetime. Simultaneously, an increase in late side effects of head irradiation has been observed.

For this reason, the adverse effects of IR on the brain have become highly interesting. The occurrence and severity of radiation-induced neurological defects including progressive

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; Ang-1, angiopoietin-1; Ang-2, angiopoietin-2; ARB, angiotensin type II receptor blockers; ARC, activity-regulated cytoskeleton-associated protein; BBB, blood-brain barrier; CNS, central nervous system; CREB, cAMP response element-binding protein; CT, computed tomography; CeVD, cerebrovascular disease; E, embryonic days; ERK, extracellular-signal-regulated kinase; ERR, excess relative risk; GABA, γ-butyric acid; Gy, gray; HNSC, human neural stem cells; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; IQ, intelligence quotient; IR, ionizing radiation; LET, Linear energy transfer; LSS, life span study; LTP, Long term potential; MAP-2, Microtubule-associated protein 2; MCH, major histocompatibility complex; MCP-1, monocyte chemoattractant protein 1; MMP, matrix metalloproteinase; NF_KB, nuclear factor kappa B; NMDA, *N*-methyl-D-aspartate; NSC, neural stem cell; PI3K, phosphoinositide 3-kinase; PPAR, peroxisome proliferator-activated receptor; PSD-95, postsynaptic density protein 95; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle; Tie-2, endothelial-specific receptor tyrosine kinase; TNF-α, tumor necrosis factor-α; UNSCEAR, United Nations Scientific Committee on the Effects of Atomic Radiation; VEGF, vascular endothelial growth factor.

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memory impairment and deficits in attention and novel-problem-solving ability tend to increase over time.

Epidemiological data raise concern on possible harmful effects of low doses of radiation in clinical screenings, for example due to computed tomography (CT) scans. Therefore, the impact of doses below 2 Gy on human health has recently attracted considerable attention. Until today no justifiable risk estimation can be defined due to the lacking data.

This review summarizes current knowledge about epidemiological and molecular effects of brain radiation ranging from low to high doses in human populations and animal and cellular experiments. It mainly deals with low linear energy transfer (LET) radiation but some high LET data from neutron or heavy ion studies have been included [4–7]. Additionally, strategies to prevent or ameliorate radiation-induced effects are being described.

2. Epidemiologic evidence of radiation-induced adverse effects on the brain

2.1. Estimated risk of brain cancer development after exposure to IR

In the second half of the 1960s, around 20,000 Israeli children were treated with X-ray therapy to eradicate tinea capitis, a disease caused by dermatophytes that invade the hair shaft, as a part of a public health campaign [8,9]. In this cohort the radiation doses to the neural tissue were retrospectively estimated for each patient with a mean of 1.5 Gy. The incidence for benign tumors was higher than that for malign ones after 40 years of follow-up. In the Swedish hemangioma study, children were exposed to doses ranging between 0.01 and 2.8 Gy [10,11]. Both studies noted a strong dose-response, an increasing health risk with decreasing age at exposure and elevated brain cancer risk with a long lag time [12]. Further, it was shown that the risk for several other cancers increased in a dose-dependent manner [13].

The Life Span Study (LSS) of Japanese atomic bomb survivors provides the best quantitative estimates for the cancer risk after low LET radiation exposure in human. It is the major source of epidemiological data used for radiation risk estimation and one of the few studies comprising of a basically healthy population of both sexes that was exposed to a wide range of radiation doses at all ages [13]. First reports about brain cancer incidence in this cohort were published in 1994 [14–17]. Over the years, brain cancer occurrence in the LSS cohort was assessed several times using longer follow-ups [18,19]. Recently, Smoll et al. reported a significant correlation between age at exposure and total cancer risk. Children exposed to irradiation showed more severe effects in general than persons exposed at adult age [20].

Interestingly, the recent risk estimates for brain cancer in the LSS cohort are substantially lower than estimates based on follow-up of children exposed to CT scans [20]. The relatively low-energy X-ray radiation used in CT imaging may increase the risk for brain cancers up to two times compared to the risk from high energy γ-rays that were the predominant exposure source in the atomic bombing in Japan [21] but more research is needed to confirm this finding.

Since 1970, the usage of CT scanning has increased in all developed countries to that extent that it is hard to imagine contemporary medicine without it. Medical X-rays including CT undoubtedly confer substantial benefits in the healthcare but at the same time they deliver radiation doses, especially after repeated application, that approach the range assumed to be able to induce adverse health effects. Cumulated doses for repeated head CT can reach the range of 40–50 mGy raising the question of possible health risks [22,23]. Many studies focusing on this question have come to controversial conclusions. Pearce and colleagues showed in a retrospective cohort study on 180,000 British children younger than 15 years at exposure a significant association between radiation doses from CT scans to brain and incidence of brain tumors [21]. According to this study, cumulative radiation doses from 2 to 3 head CTs could triple the risk of brain tumors [21]. Mathews et al. supported this observation in a study on 680,000 CT exposed Australians, reporting higher brain cancer incidence rates in scanned individuals compared to the control group. In both studies, the proportional increase in the incidence rate and the absolute excess incidence rate in the exposed group were highest 1–4 years after the first CT exposure, after which they declined. Nevertheless, brain cancer incidence was significantly increased even after 15 or more years following first exposure [24]. Huang et al. detected an increased incidence only of benign but not of malign brain tumors after pediatric CT examinations [25].

Overall, it is hard to draw a clear conclusion from the CT studies as scanning decisions are based on medical indications and are not allocated at random [26]. Thus, the possibility of reverse causation cannot be excluded, whereby early symptoms of the cancer itself may be the reason for CT scanning. Such reverse causation is especially valid for low grade cancers such as brain tumors that could lead to various symptoms years before diagnosis of cancer is made [24].

Estimated doses, number and age at exposure of people included in the epidemiological studies as well as the excess relative risk (ERR) of brain tumors as outcome of radiation exposure are summarized in Table 1.

2.2. Radiation effects on neurodevelopmental processes, cognitive function, and cerebrovascular disease

The fact that IR may impair the developing human brain and negatively affect cognition process was first documented among children exposed prenatally to the A-bomb in Hiroshima and Nagasaki [26]. Data from measurements of cognitive function, including the occurrence of severe mental retardation and

Table 1
Epidemiological studies of radiation exposure and risk estimation with confidence intervals.

Cause of exposure	Mean dose [Gy]	IR	Age at exposure	Excess relative risk (ERR)/Gy	N	References
Tinea capitis	1.5	cranial	mean 7 y	Glioma 1.98 (0.73–4.69) Meningioma 4.63 (2.43–9.12)	10,834	[4,5]
Skin hemangioma	0.07	cranial	mean 8 m	2.7 (1.0, 5.6)	28,008	[6]
Atomic bombing	0.12	whole body	≥20 y	Glioma 0.56 (0.2, 2.0) Meningioma 0.64 (0.01, 1.8) Schwannoma 4.50 (1.9, 9.2)	105,427	[9]
CT	0.035	cranial	≤ 22 y	23 (10, 49)	176,587	[17]
CT	0.049	cranial	0–19 y	15 (7, 26)	680,211	[20]

CT: Computed tomography, ERR: Excess relative risk, Gy: Gray, IR: Ionizing Radiation, M: Month, Y: Year