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Possible scenarios of the influence of low-dose ionizing radiation on neural functioning

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ABSTRACT

Possible scenarios of the influence of ionizing radiation on neural functioning and the CNS are suggested. We argue that the radiation-induced bystander mechanisms associated with Ca^{2+} flows, reactive nitrogen and oxygen species, and cytokines might lead to modulation of certain neuronal signaling pathways. The considered scenarios of conjugation of the bystander signaling and the neuronal signaling might result in modulation of certain synaptic receptors, neurogenesis, neurotransmission, channel conductance, synaptic signaling, different forms of neural plasticity, memory formation and storage, and learning. On this basis, corresponding new possible strategies for treating neurodegenerative deceases and mental disorders are proposed. The mechanisms considered might also be associated with neuronal survival and relevant to the treatment for brain injuries. At the same time, these mechanisms might be associated with detrimental effects and might facilitate the development of some neurological and psychiatric disorders.

Introduction

There has been high increase in various neurological and psychiatric disorders during the last two decades; for instance, mild forms of depression affect up to 20% of the U.S. population [1]. These disorders are supposed to originate not only from genetic but also from environmental factors. However, the mechanisms of disorders developing by environmental factors are still unclear [1]. Understanding of these mechanisms may provide opportunities to develop new strategies for the treatment for neurodegenerative deceases and mental disorders.

One of the environmental factors which may be significant in this context is low-dose ($\leqslant\sim$1 Gy) ionizing radiation. There is high worldwide increase in the population exposures to low doses of ionizing radiation [2]. Sources of low-dose radiation include medical radiation diagnostics, radiotherapy, nuclear energy plants, environmental nuclear contamination, frequent flyers and space travels. For example, most radiological examinations correspond to doses in the range from 3 to 30 mSv, individual dose in round-trip flight (New York to London) is about 0.1 mSv, and exposure on international space station is about 170 mSv per year [3].

At the same time, all living beings are instantly affected by natural ionizing radiation background. The mean levels of background radiation make up 0.2–0.3 cGy per year [4,3]. The most part (more than 50%) of the radiation background is provided by radon-222 and its radioactive decay products [5], including α-radiation (5.49 MeV) and γ-radiation (0.51 MeV) of radon-222. Importantly, there are high spatial variations of radon activity and radiation background determined by the local structure of geological medium and the intensity of the underground radon sources [6]. Also, such factors as atmospheric pressure, precipitation, humidity, temperature, and lunisolar tide affect near-surface radon activity inducing significant temporal variations of background radiation which may be comparable with its mean local levels in many regions of the Earth [6].

It should be noted that, responding to a high linear energy transfer (LET), the α-particles emitted by radon and its progeny can induce significant biological response, despite their limited tissue penetration [5]. Indeed, radon and its decay products can attach to aerosols due to electrostatic forces, so that inhaled radon and its progeny can easily penetrate into living organisms, specifically pass blood–brain barrier [5]. For example, the corresponding doses reaching the brain can be estimated as 0.21 mSv per year for inhaled radon and its decay products for concentrations of radon gas of 200 Bq/m^3 (200 Bq/m^3 is chosen as the action level by many countries), and as 0.07 mSv for ingesting water containing radon and its progeny for annual intake of 600 l of water containing 1000 Bq/l (recommended by the European Union as an action level

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for radon in private water supplies) [7]. Doses from different concentrations of radon may be obtained by linear scaling; the average dose level in the UK is about 20 Bq/m^3 for radon in air, whereas the levels in radon spas reach thousands of Bq/m^3 [5]. At the same time, radon and its progeny can reach the brain with ultrafine particles via the olfactory neural pathway, depositing in the nose and traveling along the olfactory nerve to the olfactory bulb, thus circumventing the blood–brain barrier [8–10].

There is evidence that exposures of living organisms, including humans, to low-dose ionizing radiation sources such as radiation background are able to provide physiological and pathological effects [5]. For example, Brauner et al. [10] have found significant association between long-term exposure to residential radon in a general Danish population and a risk of primary brain tumor. Specifically, background radiation from radon and its progeny in concentrations exceeded the recommended levels represents a significant public health risk [5]. Importantly, the recommended (mean) levels of radon and its decay products concentrations do not take into consideration the significant temporal variations of these concentrations, mentioned above.

It is well known that, for various cell types, radiation doses of the order of 1–10 mGy can be sufficient to produce significant biological effects such as increase of the levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS), changes in activity of a number of cell signaling pathways and alterations in gene expression, including key stress-responsive genes [17,12,18]. Bernal et al. [19] have shown that radiation exposure at doses as low as 7 mGy can alter the mice epigenome, significantly increasing DNA methylation, the effect being mediated in part by oxidative stress. Induction of chromosome inversion for whole-body irradiation of pKZ1 mouse has been shown to occur at 0.005–0.01 mGy [20]. There is evidence of health effects for uranium mining as well as non-mining cohorts exposed to background radiation [5]. Increased chromosomal aberrations have been observed both for occupational exposures and in individuals environmentally exposed to elevated background radiation in Austrian, Brazilian, Chinese, German, Russian and Slovenian populations [5]. In general, low dose radiation responses are highly dependent on genotype, cell type and tissue, but share non-linear dose–response relationship [21,18].

There is increasing evidence that low-dose ionizing radiation can influence various neuronal processes at the tissue, genetic, cell and molecular levels. Low-dose (15 cGy) whole-body γ-irradiation has been shown to change significantly brain membranes functioning, as reflected by membrane-bound acetylcholinesterase activity [22]. Changes in levels of neuroproteins following adult exposure to radiation have been reported. 500 mGy X-ray irradiation at the adult age of 45 day induces reduction in CaMKII levels in adult male mice [23]. Yin et al. [24] have shown that 10 cGy whole-body γ-irradiation (at a dose-rate of 0.64 Gy/min) modulates the transcription levels of several hundreds of genes in the adult mouse brain involved in signal transduction, ion regulation, synaptic signaling, metabolic functions, stress response, cell-cycle control and DNA synthesis/repair. The time scale of the modulation of gene expression can be less than 30 min. Lowe et al. [25] have demonstrated that the same irradiation may have effects on cognitive function. It has been shown that the mechanisms of the mouse brain response within a few hours after low-dose (10 cGy) exposure include modulation of genes associated with synapse and neuron projections [25]. Specifically, low-dose radiation modulates the expression of genes involved in a series of signaling pathways connected with axon movement and architecture (axon guidance signaling, actin cytoskeletal signaling) and metabolism (cAMP signaling, protein ubiquitination pathway, insulin receptor signaling). The mitogen-activated ERK/MAPK signaling pathway and stress-activated SAPK/JNK signaling pathway are significantly modulated after the low-dose exposures. The low-dose irradiation response involves pathways associated with neural plasticity, memory formation, and learning, including glutamate receptor signaling, G protein-coupled receptor signaling, Integrin signaling, synaptic long-term potentiation (LTP) and long-term depression (LTD) [25]. It has been shown that six neural signaling pathways associated with cognitive functions in the brain tissue of mice within a few hours after low-dose irradiation are modulated analogous to the same pathways in brain tissue of Alzheimer's patients and in brain tissue of aging humans, so that low-dose irradiation and pathologies can share common molecular stress response mechanisms [25,1]. Irradiation of mouse hippocampal neuronal HT22 cells with acute γ-dose 1.0 Gy significantly affects the expression of proteins functionally involved in Rho GDI-dissociation inhibitor signaling, actin cytoskeleton signaling, and signaling by Rho family GTPases [26]. The Rac1 protein and microRNA miR-132 levels at 0.5 Gy have been shown significantly decrease at 4 h after exposure [26]. For irradiation of male NMRI mice on postnatal day 10, similar alterations in the signaling pathways were observed in murine hippocampus and cortex 24 h after the exposure at 1.0 Gy [26]. Kempf et al. [26] suggest that acute radiation exposure leads to rapid dendritic spine and synapse morphology alterations via aberrant cytoskeletal signaling and processing. This may be associated with the immediate neurocognitive side effects observed in patients treated with ionizing radiation. Otani et al. [27] have shown that low-dose/low-dose rate ionizing radiation has a biological effect in neural cells of living animals; the most pronounced effects including up-regulation (more than 500%) of antioxidative gene peroxiredoxin-2 in the irradiated retina correspond to 650 mGy irradiation and 26 mGy/minute dose rate. Kataoka et al. [28] have shown that low-dose radon exposures can mitigate brain disorders, in particular, treatment with inhaled radon at a concentration 2000 Bq/m^3 for 24 h inhibits neuronal injury following transient global cerebral ischemia in gerbils, significantly increasing superoxide dismutase activity. Also, prior low-dose X-irradiation activates antioxidant function and inhibits cold-induced brain injury [29]. Lestaevel et al. [30] have shown that sub-chronic low-dose irradiation can result in molecular modifications of pro- and anti-inflammatory cytokines and NO-ergic pathway in the brain. In their study, rats were exposed for 3 months to drinking water contaminated with Cs-137 at a dose of 400 Bq/kg which is similar to that ingested by the population living in contaminated areas after the Chernobyl nuclear accident.

Low doses of ionizing radiation may produce changes in cognition and behavior, specifically when the exposure occurs at a young age. Study of the long-term effects of low doses of total body γ-radiation on neonatally exposed NMRI mice have shown significant alterations in spontaneous behavior at 2 and 4 months following a single 0.5 or 1.0 Gy exposure [31]. Certain alterations were revealed 6–7 months post-irradiation in the hippocampus, dentate gyrus and cortex. cAMP response element-binding protein (CREB) expression was decreased in hippocampus (~75%) and cortex (~20%) in mice treated with 1.0 Gy which may be associated with impaired neural plasticity and rapid forgetting. Reduction of the expression of plasticity related genes such as c-Fos was also observed, which is coupled to epigenetic modulation via increased levels of microRNAs (miR-132/miR-212, miR-134). Changes in the expression of genes of N-Methyl-D-aspartic acid (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, G protein-coupled glutamate receptors, protein kinases and calcium-dependent phosphatases that modulate synaptic plasticity through AMPA and NMDA receptors were observed in hippocampus and cortex. Synaptic proteins MAP-2 and PSD-95 were increased in the dentate gyrus and hippocampus (at a dose of 1.0 Gy). Signaling pathways related to synaptic actin remodeling were altered in the cortex and hippocampus. Radiation-induced