Redox Biology 9 (2016) 144–156

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Review article

The impact of high and low dose ionising radiation on the central nervous system

Calina Betlazar [a,b], Ryan J. Middleton [a], Richard B. Banati [a,b,*], Guo-Jun Liu [a,b,*]

[a] Bioanalytics group, Life Sciences, Australian Nuclear Science and Technology Organisation (ANSTO), New Illawarra Road, Lucas Heights, NSW 2234, Australia

[b] Discipline of Medical Imaging & Radiation Sciences, Faculty of Health Sciences, The University of Sydney, 75 East Street, Lidcombe, NSW 2141, Australia

ARTICLE INFO

Article history:
Received 27 July 2016
Received in revised form
6 August 2016
Accepted 9 August 2016
Available online 10 August 2016

Keywords:
Ionizing radiation
Reactive oxygen species (ROS)
Antioxidants
Neuroinflammation
Microglia
Translocator Protein (TSPO)

ABSTRACT

Responses of the central nervous system (CNS) to stressors and injuries, such as ionising radiation, are modulated by the concomitant responses of the brains innate immune effector cells, microglia. Exposure to high doses of ionising radiation in brain tissue leads to the expression and release of biochemical mediators of 'neuroinflammation', such as pro-inflammatory cytokines and reactive oxygen species (ROS), leading to tissue destruction. Contrastingly, low dose ionising radiation may reduce vulnerability to subsequent exposure of ionising radiation, largely through the stimulation of adaptive responses, such as antioxidant defences. These disparate responses may be reflective of non-linear differential microglial activation at low and high doses, manifesting as an anti-inflammatory or pro-inflammatory functional state. Biomarkers of pathology in the brain, such as the mitochondrial Translocator Protein 18 kDa (TSPO), have facilitated *in vivo* characterisation of microglial activation and 'neuroinflammation' in many pathological states of the CNS, though the exact function of TSPO in these responses remains elusive. Based on the known responsiveness of TSPO expression to a wide range of noxious stimuli, we discuss TSPO as a potential biomarker of radiation-induced effects.

Contents

1. Introduction

The impact of ionising radiation on human physiology has been documented throughout the last century, subsequent to nuclear disasters and incidents through inhalation or ingestion of radioactive material [1]. Aside from environmental exposure, artificial sources of ionising radiation are growing in utility. Currently, exposure to ionising radiation through medical diagnostics and treatment strategies now constitutes the largest proportion of average yearly radiation exposure in Australia [2]. The increasing availability and utility of ionising radiation for medical purposes warrants a reassessment of the literature on the biological impact of higher and lower doses of ionising radiation, particularly in terms of the central nervous system (CNS). Whilst the neurobiological impact of exposure to high dose ionising radiation has been well documented, the consequences of low dose exposure have garnered considerable debate [3]. Responses of biological systems

* Corresponding authors at: Bioanalytics group, Life Sciences, Australian Nuclear Science and Technology Organisation (ANSTO), New Illawarra Road, Lucas Heights, NSW 2234, Australia.
E-mail addresses: rib@ansto.gov.au (R.B. Banati), gdl@ansto.gov.au (G.-J. Liu).

http://dx.doi.org/10.1016/j.redox.2016.08.002

to ionising radiation are largely thought to follow a linear dose-response pattern [4]. Challenge to the prevailing paradigm of a linear no-threshold model comes in the form of animal radiobiological data, with several lines of evidence suggesting that exposure to lower doses of ionising radiation may confer neuroprotection [5–8]. This response has been conceptualised as radiation hormesis, where exposure to a stressor in low amounts can induce protective, radioadaptive and reparative mechanisms [9,10], though this is not without contention. Insufficient data expounding the beneficial effects of low dose ionising radiation on human physiology, and a lack of consensus regarding the definition of 'low dose', has meant that the concept of radiation hormesis is not currently acknowledged by international panels and governing bodies. Though there is still uncertainty surrounding the nature of biological responses to high and low dose ionising radiation, a more comprehensive understanding of the molecular and cellular processes underlying radiobiological responses is currently evolving [11], particularly within the context of the complex and multifaceted CNS.

Since its early discovery, radiation science has expanded in utility to medical practices [12–14], though it was not until later in history that the effects of ionising radiation on the brain were directly examined [15]. The paradox of utilising ionising radiation for therapeutic and medical diagnostic purposes is that at higher doses it may induce damage to normal tissue. The non-cancer effects of ionising radiation exposure, and the cellular reactions it can produce in the adult CNS, will be the focus of this review. In the literature, one of the more prominent manifestations of radiation-induced injury is seen in the hippocampus, a radiosensitive region housing populations of proliferating progenitor cells [16–18]. High dose irradiation can induce dysfunction or apoptosis to mature or newly born differentiating cells that integrate into the hippocampal network, manifesting as longer term functional deficits [19]. Orchestrating responses to high dose irradiation are microglial-mediated neuroinflammation and oxidative stress induced by excess reactive oxygen species (ROS) formation [20,21]. Mitochondrial redox balance and microglial responses are also critical in modulating responses to low dose irradiation, largely through the stimulation of antioxidant defences [7]. Whilst some evidence still points to a linear dose-response pattern, there is significant evidence to suggest that lower doses can confer protection to cell functioning, molecular structures, synapses, and key brain mechanisms such as neurogenesis, and induce reparative mechanisms in the face of CNS pathology [10,22]. Based on guidelines by regulatory bodies, as well as data generated by low dose radiation research programs, a low dose is considered to be acute exposure to less than 100mSv, or 0.1 Gy [23,24]. Rather than adopting a stringent demarcation between 'high' and 'low' doses of ionising radiation, we will discuss 'low dose' data within the broader range of doses up to 1 Gy, a definition which extends across many radiobiological studies.

Here we review the literature regarding the impact of ionising radiation on the CNS, highlighting remaining uncertainties surrounding the disparate responses to high and low doses of ionising radiation that are underscored by mitochondrial redox balance and neuroinflammation. This review aims to synthesise the important aspects of CNS functionality under conditions of stress, injury and pathology, which can elucidate the neurobiological responses to ionising radiation at different doses. In order to enhance understanding in this field and dissect the subcellular and molecular events that drive radiation-induced neurobiological responses, a key biomarker of CNS pathology, the mitochondrial Translocator Protein 18 kDa (TSPO), will be examined. We introduce TSPO as a novel perspective in clarifying the responses of the CNS to ionising radiation, and highlight its centrality to a comprehensive understanding of the complex network linking neuroinflammation and mitochondrial redox balance. Its utility as a sensitive *in vivo* biomarker of microglial activation, coordinating the brains innate immune response, may lead to new insights into how this process may modulate CNS responses after high and low dose irradiation, as well as elucidating the exact function of this enigmatic protein.

2. Microglial responses to stressors in the CNS

The coordination of responses to insults and stressors in the CNS are complex and multifaceted. Neurobiological mechanisms of inflammation, protection, defence and repair comprise of networks of cells and molecular mediators that respond to alterations in homeostasis [25]. Neuroinflammation is inherent to an understanding of CNS responses after such alterations, for example exposure to ionising radiation. This mechanism is distinctively characterised by the presence of activated microglia, the brains innate immune effector cells, which exhibit striking morphological and functional plasticity in response to insults [26,27]. In their resting state, microglia display highly ramified morphology and survey the microenvironment, though in the presence of endogenous or exogenous stressors, these cells can proliferate and transition morphologically to an amoeboid, activated state [28–30]. Activated microglia initiate an inflammatory response by releasing pro-inflammatory factors including cytokines and ROS [20,31]. The pro-inflammatory state of activated microglia, or the M1 type classical activation state, can be cytotoxic to surrounding cells, and when unregulated can propagate tissue damage and cause secondary injury [32,33]. Correspondingly, neuroinflammation is thought to be implicated in multifarious functions and pathological states in the CNS, including the modulation of neurogenesis and neuronal development [25,34,35], synaptic stripping and neuronal dysfunction [36,37], and is now widely implicated in the pathogenesis and progression of many neurodegenerative disorders [38–45]. Alternatively, an M2 microglial activation state is not neurotoxic, transiently conferring neuroprotection and anti-inflammatory properties in response to injury [46]. Microglial M2 activation and M2-derived factors have been demonstrated to promote remyelination and activate reparative and regenerative growth responses after lesions [47]. This activation state can also down-regulate inflammation, and reduces secondary injury which may be induced by inflammation [48], though the shift between M2 and M1 phenotypes is not well understood. The polarised activation states of microglia may also be implicated in the responses of the brain to ionising radiation, and furthermore, the disparate activation states may be reflective of the anti-inflammatory or pro-inflammatory responses of microglia after low and high dose ionising radiation, a topic which warrants future investigation.

Importantly, classically activated M1 microglia and its associated pro-inflammatory functions are intrinsically linked to the production of free radicals [20,26,49]. The production of ATP through oxidative phosphorylation results in the formation of oxidant by-products which can be damaging to cell components in sufficient quantities. The inability of antioxidant compounds and enzymes to neutralise the adverse effects of excess ROS contributes to oxidative stress, which can manifest as damage to nucleic acids, protein degradation, and lipid peroxidation in cells [50]. Concomitantly, reactive nitrogen species (RNS) and nitric oxide (NO) can also coordinate microglial responses to stressors in the CNS [51–53]. Activated microglia have also been shown to produce excess ROS and H_2O_2 from NADPH oxidases, which also generate large amounts of oxidants in activated phagocytic cells [54] and are important to the progression of ROS-mediated neuroinflammatory collateral damage to surrounding cell populations