Brain, Behavior, and Immunity 45 (2015) 287–296

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

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

Hippocampal dysfunctions caused by cranial irradiation: A review of the experimental evidence

Yeonghoon Son [a,1], Miyoung Yang [b,1], Hongbing Wang [b], Changjong Moon [a,*]

[a] Department of Veterinary Anatomy, College of Veterinary Medicine, Chonnam National University, Gwangju 500-757, South Korea
[b] Department of Physiology and Neuroscience Program, Michigan State University, East Lansing, MI 48824, USA

ARTICLE INFO

Article history:
Received 22 October 2014
Received in revised form 6 January 2015
Accepted 8 January 2015
Available online 14 January 2015

Keywords:
Cranial radiation
Hippocampal dysfunction
Neurogenesis
Neurotrophin
Neuroinflammation

ABSTRACT

Cranial irradiation (IR) is commonly used for the treatment of brain tumors but may cause disastrous brain injury, especially in the hippocampus, which has important cognition and emotional regulation functions. Several preclinical studies have investigated the mechanisms associated with cranial IR-induced hippocampal dysfunction such as memory defects and depression-like behavior. However, current research on hippocampal dysfunction and its associated mechanisms, with the ultimate goal of overcoming the side effects of cranial radiation therapy in the hippocampus, is still very much in progress. This article reviews several *in vivo* studies on the possible mechanisms of radiation-induced hippocampal dysfunction, which may be associated with hippocampal neurogenesis, neurotrophin and neuroinflammation. Thus, this review may be helpful to gain new mechanistic insights into hippocampal dysfunction following cranial IR and provide effective strategies for potential therapeutic approaches for cancer patients receiving radiation therapy.

1. Introduction

Ionizing radiation is known for its detrimental effects on the nervous system *in vivo* and *in vitro*. However, cranial radiation is the main therapeutic strategy for treating primary and metastatic brain tumors (Ewend et al., 2005; Peacock and Lesser, 2006). The neurotoxicity of cranial irradiation (IR) may be classified into acute, early delayed or late delayed brain injury according to the clinical symptoms (Greene-Schloesser et al., 2012; Tofilon and Fike, 2000). The symptoms of acute injury are expressed within days or a few weeks after IR and include fatigue, nausea and headache, but are not critical. Early delayed side effects are less frequent and related to transient demyelination, fatigue and short-term memory loss. Although these early symptoms may have more severe side effects, they are relatively rare and can resolve spontaneously. The symptoms of late delayed brain injury, which are observed 6 months or later after radiotherapy, include vascular abnormalities, demyelination, white matter necrosis and cognitive impairment. Unlike early symptoms, the late delayed effects are considered progressive and irreversible (Greene-Schloesser et al., 2012).

Cognitive impairment is one of the important side effects of cranial IR. Previous clinical studies have reported radiation-induced cognitive impairment in up to 50% of long-term brain tumor survivors (Crossen et al., 1994; Johannesen et al., 2003). Furthermore, patients treated with stereotactic radiosurgery and whole-brain radiation therapy showed significant defects in learning and memory compared with patients treated with stereotactic radiosurgery alone (Chang et al., 2009). Common symptoms of cognitive impairment induced by radiotherapy include the deterioration of verbal memory, spatial memory, attention, and novel problem-solving ability (Greene-Schloesser et al., 2012). In certain cases, radiotherapy induces other forms of brain injury, including vascular and demyelinative changes; however, memory impairment has been observed in numerous subjects who display no evidence of such pathological developments (Monje and Palmer, 2003). Therefore, a number of preclinical studies have focused on possible mechanisms during the late phase of brain injury, acknowledging that brain injuries due to radiation therapy can be influenced by patient age, total dose of IR, and combined chemotherapy. Progressive hippocampus-dependent learning dysfunction was observed in young mice at 1 and 5 months after 20 gray (Gy) fractionated cranial IR (Rao et al., 2011). Behavioral dysfunction due to fractionated IR was also found in older rats at 7 months of age using one-way

* Corresponding author at: Department of Veterinary Anatomy, College of Veterinary Medicine, Chonnam National University, 300 Yongbong-Dong, Buk-Gu, Gwangju 500-757, South Korea. Tel.: +82 62 530 2838; fax: +82 62 530 2941.
E-mail address: moonc@chonnam.ac.kr (C. Moon).
[1] The first two authors equally contributed to this study.

http://dx.doi.org/10.1016/j.bbi.2015.01.007
0889-1591/

and two-way avoidance tests (Lamproglou et al., 1995). Raber and colleagues (2004) found hippocampus-dependent spatial learning and memory impairments were induced by a single dose of 10 Gy, which was equivalent to 10 2-Gy fractionated doses, without structural changes in the brain region. In addition to these studies, various reports have shown radiation-induced memory deficits using various behavioral paradigms (Table 1).

Depression symptoms as well as cognitive impairments tend to occur more often in cancer patients than in the general population (van't Spijker et al., 1997), suggesting an important relationship between depression and survival among cancer patients. Furthermore, over 17 years of follow-up, the mortality rate for depressed cancer patients was twice as high as for other cancer patients (Shekelle et al., 1981), indicating the importance of managing depression during cancer treatment. The symptoms of depression cover a broad spectrum ranging from sadness to major affective disorder, with the most common symptoms being depressed mood, insomnia, and fatigue (Massie, 2004). It is particularly difficult to establish the causes and mechanisms associated with depression following IR cancer treatment, since cancer diagnosis is associated with highly negative cognitions with regard to treatments, and could affect psychiatric comorbidity prior to cancer therapy (Pereira Dias et al., 2014). Therefore, experimental models have been careful in their investigations of depressive symptoms as possible side effects of cancer therapy. In preclinical studies, the presence of a peripheral tumor and chemotherapy were each deemed to be sufficient to cause behavioral brain dysfunction such as memory impairment and depression-like behavior, possibly due to altered molecular and cellular hippocampal parameters (Yang et al., 2010, 2011, 2012a,b, 2014). Hippocampal neurogenesis is one possible mechanism for the occurrence of emotional problems in experimental animals, because cranial irradiation decreases the rate of neurogenesis in adult rodent hippocampus, as shown in Table 1. Decreased neurogenesis has been implicated in the pathogenesis of anxiety and depression, as measured by the tail suspension test, the forced swimming test, and the sucrose preference test for anhedonia (Snyder et al., 2011). Consistent with clinical studies reporting depression symptoms following cranial radiotherapy, animal research has also reported the occurrence of emotional problems after irradiation. Recently, several papers have found detrimental effects of cranial IR on emotional regulation. For example, preclinical studies showed that depression-like behaviors were induced in the late phase after cranial IR (Dulcich and Hartman, 2013; Son et al., 2014). However, a previous study reported no significant alteration in depression-like behavior using the tail suspension test (TST), and only modest effects were detected during initiation of the behavioral task (Wong-Goodrich et al., 2010). Thus, the appearance of depression-like behavior after cranial IR remains controversial, and more comprehensive studies regarding emotional regulation are needed in the future.

Recently, research has increasingly focused on the relationship between emotion and cognition (commonly referred to as the emotion–cognition interaction) and between motivation and cognition (Chiew and Braver, 2011; Crocker et al., 2013; Pessoa and Engelmann, 2010; Phelps, 2006). Since emotion and motivation are closely related, and motivation has strong links to cognition (Chiew and Braver, 2011), the depressive phenomena observed in cancer patients and in animals may play a causal role in radiation-induced cognitive impairment. However, most preclinical research of radiation-induced memory impairment has taken care to establish comparable levels of motivation before and after radiation prior to measuring performance on cognitive tasks. This can be done with experimental animals, for example, by comparing locomotor activity in an open field, or by measuring swimming speed or performance during visible-cue trials in the Morris water maze (Ji et al., 2014; Rola et al., 2004). Although motivation levels in these studies appear to be comparable in the pre- and post-irradiation phases, allowing for the appropriate evaluation of cognitive function following irradiation, the precise connections between motivation, depression and cognitive impairment following IR have yet to be addressed.

The radiotherapy protocol in humans varies depending on factors such as tumor size, location, metastasis, and age. For intra-cranial radiation, a multiple-dose fractionation regimen is commonly used (e.g., 20 Gy in 5 or 8 fractions, 24 Gy in 12 fractions, 25 Gy in 10 fractions or 30 Gy in 10 or 12 fractions) (Laack and Brown, 2004; Slotman et al., 2007), with a single higher-dose regimen (around 20 Gy) used for brain metastases (Kocher et al., 2014; McTyre et al., 2013). However, studies have reported various risk factors for developing neurological complications, including cognitive disability, after radiotherapy: age (<7 or >60 years), the hyperfractionation schedule, the volume of the irradiated brain, and the dose per fraction (>2 Gy) (Dietrich et al., 2008; Klein et al., 2002; Taphoorn and Klein, 2004). Thus, various preclinical studies have used comparable protocols that are commonly utilized in the clinic, such as the single fractionation of high-dose (Chiang et al., 1993; Hong et al., 1995; Son et al., 2014) or multiple-dose fractionation regimens (Lamproglou et al., 1995; Rao et al., 2011) to identify the side effects of cranial radiation and to investigate the precise mechanisms of radiation-induced dysfunction. However, further studies are necessary to elucidate the etiology of injury to normal brain tissue due to cranial IR and to develop therapeutic treatments for reducing the side effects of cranial IR. Thus, in this review we provide an overview of possible behavioral impairment mechanisms following cranial IR and discuss the possible strategies for developing preventive or therapeutic agents that ameliorate the side effects of brain radiation therapy.

2. Cellular and molecular mechanisms of hippocampal dysfunction caused by cranial irradiation

2.1. Hippocampal neurogenesis

The hippocampus, a critical region in the medial temporal lobe, plays a role in the formation of spatial and episodic memory (Eichenbaum et al., 1999). The subgranular zone of the dentate gyrus (DG) is one of two regions that produce new neurons throughout life in the adult brain (Altman and Das, 1965). A dose-dependent decrease in hippocampal neurogenesis was demonstrated by irradiating the rodent brain (Mizumatsu et al., 2003; Monje et al., 2002), which has been used to deplete neurogenesis and to examine the role of newly-generated cells in a variety of studies (David et al., 2009; Wojtowicz, 2006). A single X-ray dose of 10 Gy, a dose that does not induce demyelination or white matter necrosis (Hodges et al., 1998; Monje et al., 2002), resulted in depletion of the majority of proliferating cells in adult mice DG 3 months after cranial IR, correlating with cognitive deficits using the Barnes maze test (Raber et al., 2004). Decreased hippocampal neurogenesis and hippocampus-dependent memory dysfunction were also reported in young mice (21-day-old) 3 months after a single X-ray dose of 5 Gy (Rola et al., 2004).

Hippocampal neurogenesis is reportedly implicated in emotional regulation, although the role of hippocampal neurogenesis in mood disorders has been debated (Sahay and Hen, 2007). Animal models of depression have shown decreased hippocampal neurogenesis which was suggested as a possible mechanism in depressive disorders (Vaidya et al., 2007). Additionally, a previous study demonstrated that mice exposed to 2 Gy proton radiation displayed depression-like behaviors compared with non-irradiated mice 2 months after IR (Dulcich and Hartman, 2013). These results are consistent with a recent study showing that 10 Gy single cra-