Experimental Neurology xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Experimental Neurology

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

Review

Hyperbaric oxygen therapy: Can it prevent irradiation-induced necrosis?

Damien P. Kuffler *

Institute of Neurobiology, University of Puerto Rico, Medical Sciences Campus, Puerto Rico

ARTICLE INFO

Article history:
Received 17 January 2012
Revised 27 February 2012
Accepted 17 March 2012
Available online xxxx

Keywords:
Necrosis
Inflammation
Angiogenesis
CNS
HBOT
Human
Hyperbaric oxygen therapy
Irradiation
Tumors
Non-steroid anti-inflammatory drugs
NAIDs
Prostaglandin
Delayed irradiation side effects

ABSTRACT

Radiosurgery is an important non-invasive procedure for the treatment of tumors and vascular malformations. However, in addition to killing target tissues, cranial irradiation induces damage to adjacent healthy tissues leading to neurological deterioration in both pediatric and adult patients, which is poorly understood and insufficiently treatable. To minimize irradiation damage to healthy tissue, not the optimal therapeutic irradiation dose required to eliminate the target lesion is used but lower doses. Although the success rate of irradiation surgery is about 95%, 5% of patients suffer problems, most commonly neurological, that are thought to be a direct consequence of irradiation-induced inflammation. Although no direct correlation has been demonstrated, the appearance and disappearance of inflammation that develops following irradiation commonly parallel the appearance and disappearance of neurological side effects that are associated with the neurological function of the irradiated brain regions. These observations have led to the hypothesis that brain inflammation is causally related to the observed neurological side effects. Studies indicate that hyperbaric oxygen therapy (HBOT) applied after the appearance of irradiation-induced neurological side effects reduces the incidence and severity of those side effects. This may result from HBOT reducing inflammation, promoting angiogenesis, and influencing other cellular functions thereby suppressing events that cause the neurological side effects. However, it would be significantly better for the patient if rather than waiting for neurological side effects to become manifest they could be avoided. This review examines irradiation-induced neurological side effects, methods that minimize or resolve those side effects, and concludes with a discussion of whether HBOT applied following irradiation, but before manifestation of neurological side effects may prevent or reduce the appearance of irradiation-induced neurological side effects.

Contents

* Corresponding author at: Institute of Neurobiology, 201 Blvd. del Valle San Juan, PR 00901, Puerto Rico. Fax: +1 787 725 1289.
E-mail address: dkuffler@hotmail.com.

0014-4886/$ – see front matter © 2012 Published by Elsevier Inc.
doi:10.1016/j.expneurol.2012.03.011

Introduction

Since 1987, more than 500,000 patients in North America have undergone stereotactic radiosurgery, subsequently referred to as irradiation, for the management of a variety of brain disorders, including tumors, vascular malformations, pain, movement disorders and epilepsy. Irradiation is now considered a mainline intervention and is often used as an alternative to more conventional invasive neurosurgical procedures.

Irradiation-induced inflammation, tissue necrosis and neurological deficits

Whole brain radiation carries the serious risk of neurotoxicity in about 90% of patients, with the extent of tissue necrosis increasing with the increasing volume of radiated tissue. However, the extent of tissue necrosis and the severity and types of side effects induced by irradiation can be reduced by using focal irradiation such in stereotactic Gamma Knife surgery.

When following irradiation, the irradiated site is examined using T2-weighted magnetic resonance images (MRI), 36% of patients manifest an increased signal around the irradiation site (Mahadevan et al., 2011; Yen et al., 2010). Clinically this signal is generally interpreted as irradiation-induced brain inflammation changes associated with tissue swelling, neuron death and neurological losses (Son et al., 2001; Stancanello et al., 2009; Wanebo et al., 2009; Wu et al., 2009; Yen et al., 2010). The appearance and disappearance of inflammation seen in T2-weighted magnetic resonance images are frequently associated with the appearance and disappearance of necrosis (Stancanello et al., 2009; Yen et al., 2010). This observation led to the hypothesis that irradiation-induced inflammation underlies, or is causally related to, the appearance and disappearance of tissue necrosis and the manifestation of neurological deficits.

Depending on the tissue irradiated and the extent of tissue necrosis that develops, various side effects and neurological deficits may manifest including mental deterioration, progressive dementia, loss of memory, headache, fatigue, nausea and vomiting sleepiness, dry-mouth, altered sense of taste, blurry vision, loss of hearing and ataxia (Chan et al., 2003; Chin et al., 2000; Tuan et al., in press). However, when irradiation is used to destroy tumors, such as Schwannomas, intimately associated with nerves, such as the trigeminal, optic, occulomotor, olfactory or acoustic, the irradiation can lead to nerve demyelination and degeneration, fragmentation, or loss of axons (Vernimmen et al., 2009; Yeung et al., 2009). This nerve damage can result in even greater neurological deficits since the neurological functions of the damaged nerves are permanently lost causing deafness, loss of taste, blindness, and with trigeminal nerve damage, the loss of sensation in the face, and certain motor functions such as biting, chewing, and swallowing (Akamatsu et al., 2010; Arvold et al., 2009; Dea et al., 2010; Lesser et al., 2010; Petsuksiri et al., 2011; Vernimmen et al., 2009; Zakrzewska and Akram, 2011). The presence of necrosis can be documented by performing biopsies on the irradiated tissue areas (Chuba et al., 1997). Radiation-induced necrosis is generally considered irreversible (Delanian and Lefaix, 2004; Przybyszewska et al., 2011; Wang et al., 2009).

Following the manifestation of irradiation-induced necrosis, the major clinical interventions are steroid treatment, decompression, and hyperbaric oxygen therapy (Djalilian et al., 2007; Foroughi et al., 2010; Narozny et al., 2005; Spiegelberg et al., 2010). However, additional methods will also be discussed that can be used in attempts to slow or block the manifestations of inflammation and necrosis.

Presently there is no way of anticipating which irradiated patients will manifest irradiation-induced inflammation and neurological side effects (Wanebo et al., 2009). Therefore, clinically one is forced to wait and see which patients manifest inflammation, tissue necrosis and neurological deficits. Of brain irradiated patients who show edema, 33% are asymptomatic for clinical manifestations of neurological deficits (Geraci et al., 1993). However, even though irradiation induces significant peritumoral cerebral edema, or a worsening of a preexisting edema, reducing the edema results in a better quality of patient life, but not longer patient survival (Kosower et al., 1980).

Irradiation-induced inflammation and normal brain tissue necrosis are the main risk factors associated with brain irradiation, with the neurological side effects being more frequent and appearing earlier following higher total irradiation doses and at higher doses per fraction (Clavo et al., 2009). Irradiation-induced brain injury is a complex and dynamic process involving all cells in the brain, including endothelial and oligodendroglial cells, astrocytes, microglia, neurons, and neuronal stem cells. The symptoms of irradiation-induced brain injury may be acute, subacute, or chronic, occurring hours, days, weeks, months, and even years after irradiation exposure (Butler et al., 2006). Because of the increasing application of irradiation, and the fact that irradiated patients survive for many years following irradiation, its potential risks and benefits have become more widely known, especially for cases in which the damage is manifest only at long times, up to years, post irradiation. Therefore, rather than wait for irradiation-induced necrosis to become manifest, it is important to identify methods that can prevent, reduce or eliminate irradiation-induced triggers that lead to tissue damage and thereby prevent the development of necrosis.

Only a few techniques are currently used clinically for providing protection against irradiation-induced brain injury, and these involve a multidisciplinary approach using pharmacologic, behavioral, and rehabilitative therapies. However, given the prevalence of brain neoplasms and the high incidence of irradiation-induced negative symptoms, more clinical research is essential to address these important clinical problems.

This review starts with an examination of neurotoxic factors associated with irradiation, including cytokines, prostaglandins (PGs), and nitric oxide (NO) that lead to inflammation, neurotoxicity and neurological side effects. It then discusses methods that reduce irradiation-induced changes, and an examination of evidence indicating

Please cite this article as: Kuffler, D.P., Hyperbaric oxygen therapy: Can it prevent irradiation-induced necrosis? Exp. Neurol. (2012), doi:10.1016/j.expneurol.2012.03.011

that hyperbaric oxygen therapy (HBOT) can counter the development of acute and long-term post irradiation irradiation-induced pathophysiological events and inflammation in particular. It is concluded that the abundance of evidence indicates that HBOT is an effective therapy for reducing irradiation-induced delayed tissue irradiation damage, (Al-Waili et al., 2005a, 2005b; Chuba et al., 1997; Cihan et al., 2009; Feldmeier et al., 1995; Kohshi et al., 2003) with no convincing evidence that it enhances or stimulates malignant growth (Al-Waili et al., 2005a, 2005b; Feldmeier, 2004a, 2004b). Finally it is suggested that it may be more efficacious to apply HBOT before rather than after irradiation-induced side effects become manifest.

Mechanisms of irradiation-induced neurotoxicity

Chromosomal damage

Irradiation induces chromosomal aberration that result in cell death, with the extent of tissue radiosensitivity dependent on cell-cycle-stage dependent DNA damage and repair (Terzoudi et al., 2011). Irradiated human blood born cells undergo DNA double-strand breaks (DSB), which are a cytotoxic form of DNA damage, that if not correctly repaired triggers genomic instability, chromosome aberrations, mutations or apoptosis (Ghardi et al., in press). The apoptotic DNA fragmentation increases in a dose-dependent manner. In the mouse, irradiation-induced chromosomal instability develops in both targeted and non-targeted cells, and is characterized by an increased rate of chromosome aberrations many generations after the initial insult and having pathological consequences. This chromosomal instability is a consequence of inflammatory processes which contribute to secondary damage expressed as delayed non-targeted tissue irradiation damage (Mukherjee et al., 2012).

Chromosomes and gene expression

Irradiation of the mouse leads to large changes in the expression of induced and repressed genes compared to what is seen in non-irradiated animals (Hirano et al., 2009; Nordal and Wong, 2005). The irradiated gene expression serves to promote the cell survival and invasion of tumor cells, and the development of angiogenesis, which also favors tumor survival (Kargiotis et al., 2010).

Direct irradiation of the mouse cell nucleus contributes to genomic instability, chromosome aberrations, DNA fragmentation, mutations or apoptosis, which may be permanent or that can be repaired (Covo et al., 2012; Mukherjee et al., 2012). However, non-irradiated cells also undergo DNA damage that results from cell signaling, which is part of an inflammatory process that causes an increased rate of chromosome aberrations for many generations after the initial insult leading to delayed radiation effects with pathological consequences (Mukherjee et al., 2012).

Irradiation of the mouse hippocampus results in the rapid, within 24 h, upregulation of the genes for metallothioneins (MT)-I and -II, heat shock protein (Hsp-27), glial fibrillary acidic protein alpha (GFAP), and c-Fos, which may underlie the appearance of cognitive changes in humans following cranial irradiation (Achanta et al., 2007). Irradiation of the whole mouse brain alters the expression patterns of more than 1500 genes, of which 855 show more than a 1.5-fold change in expression (Yin et al., 2003). Among the effects of these alterations are changes in neuron ion regulation, synaptic signaling, metabolic functions including myelin and protein synthesis, stress response, cell-cycle control and DNA synthesis/repair (Yin et al., 2003).

Clinically, irradiation induces the down-regulation of genes including cyclins (cyclin-dependent kinase inhibitor 1A (CDKN1A), cyclin G1 (CCNG1)), sestrin 1 (SESN1), growth arrest and DNA damage inducible 45 alpha (GADD45A), ferredoxin reductase (FDXR), p53 up-regulated mediator of apoptosis (BBC3) and Mdm2 p53 binding protein homolog (MDM2), centromeric and mitotic checkpoint genes, particularly those associated with chromosome instability and cancer (Kabacik et al., 2011).

A study of gene expression in a leukemia cell line found that irradiation leads to increased expression of hundreds of genes, especially those involved in cell cycle checkpoints and their regulation (CDKN1A), DNA repair (GADD45A, DDB2, XPC), apoptosis induction (DR5, FasR, Apo-2L, Bax), and T-cell activation/proliferation (CD70, OX40L) (Lindgren et al., in press). Cell death is then caused by induced apoptosis and an increased activation of initiator (caspase-8 and caspase-9) and execution (caspase-3) caspases (Lindgren et al., in press). However, irradiation also leads to the upregulation of Vn receptor integrins, which results in increased glial cell mobility, which in turn facilitates their invasion of healthy brain tissue (Rieken et al., 2011). Other genes for which irradiation increases their expression are the heat shock protein 5 (HSP 5), HSP 90 kDa beta, HSP 1, and phosphoglycerate kinase 1 (PGK1) and down-regulation of transaldolase 1 (TA1), (Lim et al., 2011), all of which enhance the survival of tumor cells. Finally, irradiation leads to the alteration of several genes for oxidative stress, antioxidants defense mechanism, ROS metabolism, and oxygen transporters related genes expression, leading to DNA damage, followed by cell death (Kargiotis et al., 2010).

Inflammation by increased vascular and blood brain barrier permeability

In rats, although venous structures are considered radioresistant, irradiation of endothelial tissue causes vesicular dysfunction involving increased transport across the endothelium of the blood–brain barrier (BBB) without opening the tight junctions, leukocyte–endothelial interactions, astrogliosis, perivascular edema, endothelial cell apoptosis, collapsed microvascular, venous flow stasis and premature venous occlusion (early draining vein occlusion) (Cicciarello et al., 1996; d'Avella et al., 1998; Griem et al., 1994; Nordal and Wong, 2005; Sabatasso et al., 2011; Wanebo et al., 2009; Zawaski et al., in press). In mice these irradiation-induced changes result in part from a sustained multiphasic inflammatory response within minutes (Sabatasso et al., 2011) to hours (Liu et al., 2010), and which increase over the subsequent days to weeks (Adamson and Bowden, 1983; Cicciarello et al., 1996). This suggests a possible association between damage of the microvascular/glial unit of tissue injury and the development of irradiation-induced brain toxicity (Cicciarello et al., 1996).

Inflammatory cell recruitment, activation and cytokine release

Radiation-induced cranial damage is characterized by loss of parenchymal cells and excessive formation of fibrous tissue. This is a dynamic process in both its temporal sequence and actions, and is associated with the acute recruitment and activation of a variety of cells including astrocytes, microglia and inflammatory macrophages, from proliferating resident precursors and recruitment of blood-borne progenitors, respectively, lymphocytes, neutrophils, fibroblasts, glia, and both epithelial and endothelial cells (Ajami et al., 2011; Johnston et al., 2004; Moravan et al., 2011). Then, by 1 month after irradiation there is an increase in T cells, MHC II-positive cells, and CD11c-positive cells (Moravan et al., 2011). This cell recruitment is in part due to cranial irradiation leading to increased TNF activity, which causes increased BBB permeability, which in turn allows for leukocyte infiltration (Wilson et al., 2009). However, leukocyte infiltration can be significantly reduced by preventing the irradiation-induced increase in BBB by blocking TNF activity with an antibody against TNF (Wilson et al., 2009). Once recruited, these cells result in the secretion of a number of proinflammatory cytokines, profibrotic cytokines, and chemokines produced by a variety of cell types, including macrophages, epithelial cells, and fibroblasts (Anscher and Vujaskovic, 2005). These events can continue for months or years after irradiation.

Whole body rat and mouse irradiation significantly increases the transcription and released of proinflammatory mediators, including

Please cite this article as: Kuffler, D.P., Hyperbaric oxygen therapy: Can it prevent irradiation-induced necrosis? Exp. Neurol. (2012), doi:10.1016/j.expneurol.2012.03.011

tumor necrosis factor-alpha (TNF-alpha), a pro-inflammatory cytokine, (Lee et al., 2010; Linard et al., 2004; Rosi et al., 2008; Schilling and Eder, 2011) NO, matrix metalloproteinases (MMP), reactive oxygen species (ROS), (Moravan et al., 2011; Zhu et al., 2009) NF-kappaB, a transcription factor that regulates microglial activation (Hayakawa et al., 1997; Hwang et al., 2006), activator protein-1 (AP-1), cAMP response element-binding protein (CREB) and a minimal enhancement of TGF-beta1 mRNA (Hayakawa et al., 1997). The CCR8 ligand, TCA3, is produced predominantly by resident microglia in response to TNF, and TCA3-CCR8 interactions contribute to rapid-onset central nervous system (CNS) inflammation. Chemokines are a major, although not exclusive, mechanism by which tissues regulate leukocyte movement in response to TNF (Murphy et al., 2002). Thus, irradiation-activated cells release proinflammatory cytokines (Dong et al., 2009) that are associated with a reduction in neuron activity (Hwang et al., 2006; Vollmann et al., 2007) and neurotoxicity (Liu et al., 2010).

In vitro, glia cytokine release is in part induced by an elevation of microglia intracellular calcium concentration (Drew and Chavis, 2000; Farber and Kettenmann, 2006) triggered by glial activation by the neurotrophin brain-derived neurotrophic factor (BDNF) (Mizoguchi et al., 2011). The extent of astrocyte, oligodendrocyte and endothelial cell activation and proliferation is irradiation dose-dependent, as is the pathogenesis of irradiation-induced tissue damage and neurotoxicity (Chiang et al., 1993; Dong et al., 2009; Moravan et al., 2011; Vollmann et al., 2007). Thus, cranial irradiation of rats leads to persistent vascular permeability and neuroinflammation, called a chronic inflammatory response, (Liu et al., 2010) due to albumin extravasation staring immediately after irradiation exposure (Celix et al., 2009; Eberhardt et al., 2008; Matuschek et al., 2011; Nittby et al., 2009; Velickovic et al., 2009) and reduced neuronal activity (Chiang et al., 1993; Hwang et al., 2006).

In the normal cerebral cortex the cyclooxygenase Cox-2 is present in neurons, but not glial or vascular endothelial cells. However, whole irradiation of the rat brain induces a dose-dependent increase in mRNA levels for Cox-2, interleukin(IL)-1beta, IL-6, IL-18, TNF and interferon-gamma-inducible protein-10, normally associated with microglia activation, (Hwang et al., 2006) and human monocyte chemoattractant protein-1 (MCP-1) (Lee et al., 2010). The enhanced release of Cox-2 from irradiated human microglia plays a key role in the development of edema and immunomodulation (Temel and Kahveci, 2009) by causing irradiated microglia to produce prostaglandin-E2 (PG-E2), a metabolic product of the Cox-2 enzyme, a key mediator of irradiation-induced gliosis or astrocyte phenotype change (Hwang et al., 2006). These data suggest that irradiation-induced microglial activation and their resultant production of PGE2 are associated with an underlying cause of inflammatory complications associated with irradiation therapy.

Although inflammation does not significantly induce neuron death by itself, for cultured neurons, inflammation plus amyloid-beta, or amyloid-beta protein precursor, induces a significant increase in neuron death, and a 6-fold increase in the production of interleukin 1beta (IL-beta1) (Ramirez et al., 2008). This neurotoxicity is a slow process, which depends on activated microglia and additional stimuli, whereby an elevated concentrations of interleukin 1beta (IL-1beta) and radical species, along with decreased secretion of neuroprotective cytokines, such as transforming growth factor beta1 (TGFbeta1), that plays a central role in the pathogenesis of inflammatory responses (Flanders et al., 2002), and supports persistent activation of glial cells and cell damage (Ramirez et al., 2008).

Cranial irradiation can lead to cognitive deficits, that often include significant impairments in hippocampus-dependent function such as learning, memory, and spatial information processing (Osato et al., 2010; Raber et al., 2004; Rola et al., 2004; Winocur et al., 2006). These cognitive deficits are most extensive when the irradiation is to the medial temporal lobes (Ben Abdallah et al., 2007). But deficits also result from irradiation-induced depletion of stem/precursor cell pools particularly those in the neurogenic region of the hippocampus (Linard et al., 2004), the loss of neural stem and progenitor cells (Kalm et al., 2009), and inflammation (Son et al., 2006). This hypothesis is supported by data showing that if 2 days following cranial irradiation, human embryonic stem cells (hESC) are implanted into the hippocampus of mice, by 4 months later their cognitive deficits are less than those of mice that do not receive implanted cells (Linard et al., 2004).

Techniques (other than HBOT) that reduce irradiation-induced neurotoxicity

For patients suffering comparatively mild irradiation side effects, some relatively straight forward approaches can minimize their manifestation. In the case of fatigue this might include getting at least 8 h of sleep, minimizing activities and exercise, while for hair loss nothing can be done except to wait for new hair to grow. In the case of irradiation-induced mouth problems, maintaining good oral hygiene is the optimal approach, while for nausea and diarrhea, changing to a bland diet may help. However, for the more severe neurological side effects, there is little a patient can to reduce the manifestations of the side effects. Dealing with these side effects requires clinical interventions. Following is a discussion of techniques that reduce neurotoxicity and preserve neurological function following the onset of irradiation-induced neurotoxicity. The aims of these approaches are to prevent microglia and macrophage infiltration, activation, and their release of factors with neurotoxic influences (Lee et al., 2011; Wang et al., 2005).

Steroid therapy

Following the appearance of inflammation and necrosis within the irradiated region of the brain and the appearance of neurological side effects, the first line of patient treatment is to control acute and chronic inflammation with steroid therapy, using drugs such as dexamethasone or cortisol, glucocorticoid steroid hormones (Blomstrand et al., 1975; Dea et al., 2010; Delanian and Lefaix, 2007; Drew and Chavis, 2000), or interferon gamma (Delanian and Lefaix, 2007). If these treatments are not successful, alternative approaches can be used.

Non steroid anti-inflammatory drugs (NSAIDs)

Clinically and in animal models, non-steroid anti-inflammatory drugs (NSAIDs) provide radioprotection (Grombacher et al., 1996). Since cells in the mitotic (M) and late G2 phases of the cell cycle are more sensitive to radiation than cells in the early S and G1/G0 phases, and NSAIDs shift cells toward a quiescence state (G0/G1) in which they are less sensitive to irradiation damage, they provide protection against irradiation (Lee and Stupans, 2002; Mattern et al., 2007). NSAIDs also act by elevating the level of superoxide dismutase in cells and activate heat shock proteins, thereby increasing cell survival by changing cytokine expression (Mattern et al., 2007).

PGE does not regulate the cell cycle, but effect cell growth and differentiation by inducing angiogenesis (Mattern et al., 2007). PGE (Vlodavsky et al., 2006) also increases cell survival by inhibiting pro-inflammatory cytokines such as TNF-alpha and IL-1beta, thereby reducing inflammation (Lee and Stupans, 2002; Mattern et al., 2007; Mizoguchi et al., 2011).

Blocking the release of neurotoxic cytokines and nitric oxide synthesis

In vivo mice and in vitro experiments on animal and human cells have shown that increased intracellular calcium is critical for microglial functions, and their synthesis of inducible nitric oxide synthase (iNOS), which catalyzes the synthesis and release of NO and neurotoxic cytokines, such as TNF-alpha, IL-1beta, and IL-6, and the neurotrophic factor BDNF, that are associated with high rates of mortality and morbidity (Farber and Kettenmann, 2006; McLarnon et al., 2001; Yamashita et al., 2006). Human and mice microglia activation and their associated

Please cite this article as: Kuffler, D.P., Hyperbaric oxygen therapy: Can it prevent irradiation-induced necrosis? Exp. Neurol. (2012), doi:10.1016/j.expneurol.2012.03.011

neurotoxicity can be prevented by reducing or blocking microglial intracellular calcium increases by the use of inhibitors of L-type voltage-sensitive calcium channels, such as verapamil, nifedipine and diltiazem (Silei et al., 1999; Toescu et al., 1998).

Glial activity can also be modulated by tricyclic antidepressants clomipramine and imipramine, which exert anti-inflammatory and neuroprotective effects in the CNS (Hwang et al., 2008). They act in part by inducing cultured microglia and astrocytes to significantly decrease their production of NO, and neurotoxic cytokines (Hwang et al., 2008). They also inhibit IkappaB degradation in stimulated microglia cells (Hwang et al., 2008).

Neuroprotection against irradiation of mice can also be accomplished by the administering perillic acid, which reduces the level of proinflammatory cytokines such as IL-1beta, TNF-alpha and CRP, which are elevated during irradiation (Pratheeshkumar et al., 2010). However, inhibiting TNF-alpha or COX-2, two dominant inflammatory pathways, is not effective in preventing irradiation-induced responses in some tissues (Haagen et al., 2009).

Reducing endothelial permeability

Both clinically and in the mouse, irradiation leads to a rapid and sustained increase in microglia activation and their release of IL-1 beta and TNF-alpha leading to a chronic inflammatory response (Liu et al., 2010). Tamoxifen administration immediately following irradiation significantly inhibits the irradiation-induced microglial inflammatory response and brain damage. Thus, tamoxifen can decrease the irradiation-induced brain damage via attenuating the microglial inflammatory response (Liu et al., 2010).

Inflammatory agents, including serotonin (5HT), increase endothelial permeability and vessel diameter, which lead to a significant leak across the BBB and the formation of cerebral edema (Abbott, 2000; Westergaard, 1978). Clinically and in animal models, reducing 5HT activity reduces endothelial cell permeability and thus inflammation (Abbott, 2000; Chang et al., 2006; Sun et al., 2010; Veltkamp et al., 2005).

In vitro, NF-kappaB is involved in the activation of cerebral microvascular endothelial cells and causes increased permeability, monocyte transmigration and inflammation. Inhibition of NF-kappaB activation prevents these endothelial cell changes (Gonzalez-Velasquez et al., 2011; Lee et al., 2006a, 2006b; Min et al., 2007).

Antibodies

The neurotoxicity of human and mouse neurons in vitro caused by various neurotrophic factors can be reduced by almost 40% by the administration of antibodies that specifically target and neutralize these factors (Lee et al., 2011; Sakaue et al., 2009; Wang et al., 2005). Clinically, the neurotoxicity induced by TNF is due to its initiation of acute damage to the BBB and brain tissue following irradiation, can be reduced in an animal model and for isolated human cells by treatment with an antibody against TNF, which leads to significantly reducing BBB permeability, leukocyte adhesion and the number of activated astrocytes by 24 post irradiation (Wilson et al., 2009; Xiao et al., 2011). Thus, following irradiation, treatment with an antibody against TNF protects the brain's microvascular network from the acute damage.

The development of irradiation-induced neurotoxic edema, caused by increased capillary permeability, and triggered by the cytokine vascular endothelial growth factor (VEGF), can be completely abolished clinically and in the rat by bevacizumab, an antibody that neutralizes VEGF (Bills et al., 2011; Gronier et al., 2011; Matuschek et al., 2011; Mihalcea and Arnold, 2008; Shi et al., 2011; Torcuator et al., 2009). Clinically this leads to a decreased vascular permeability and improvements in neurologic signs and symptoms (Fischer et al., 1999). These improvements are associated with a decrease in T1-weighted signal, indicating that it is associated with a decrease in tissue inflammation.

Cox-2 inhibitors

Following irradiation of rat cells in culture, the neurotoxicity of prostaglandin (PG) can be reduced by about 16% by treatment with the Cox-2 inhibitors acetylsalicylic acid, ibuprofen and Quercetin (Rodriguez-Gonzalez et al., 2011; Xiao et al., 2011), while the toxicity caused by oxidative stress, mediated by the generation of ROS can be reduced by almost 20% by blocking production with the NADPH inhibitor diphenylene iodonium (DPI) (Lee et al., 2011; Xiao et al., 2011). The neurotoxicity of cultured human monocytes caused by NO can be reduced by 20% by treatment with the NO scavenger carboxy-phenyl-tetramethylimidazolineoxyl-oxide, or the NOS inhibitor N(G)-monomethylene-L-arginine (Lee et al., 2011).

Glutamate channel blockers

Irradiation-induced glutamate neurotoxicity of isolated human monocytes can be reduced by 13% by removing the released glutamate by glutamate decarboxylase (Lee et al., 2011). Glutamate-induced apoptotic death of rat retinal ganglion cells (RGCs) can be prevented by blocking the dihydropyridine-type calcium channel blocker, which in turn blocks calcium influx via voltage-dependent calcium channels in purified RGCs (Otori et al., 2003). Veratrine, which blocks the voltage-dependent sodium channel, prevents glutamate induced neurotoxicity of isolated rat primary cultured cells, although it is not clear whether it acts as a channel blocker of by another mechanism (Shimojo et al., 1999). For neurons in rat organ cultures, TNF alpha, at a high (3.3 mM) but not low (20 ng/ml) dose, significantly potentiates and accelerates glutamate neurotoxicity, by inhibiting glutamate uptake, but the glutamate toxicity can be blocked by NMDA receptor agonists (Zou and Crews, 2005). Excitatory synaptic efficacy and thereby glutamate excitoxicity in rats can be blocked by inhibition of the glutamate transporter-1 (GLT-1) activity, the predominant glutamate transporter (Niederberger et al., 2003). For rat RGCs, arachidonic acid (AA), an intercellular messenger, reduces irradiation-induced neurotoxicity by inhibiting non-NMDA ionotropic receptors (Kawasaki et al., 2002).

Blocking induced apoptosis

Within 24 h of cranial irradiation, vascular endothelium damage is induced and is accompanied by a 15% apoptotic loss of rat endothelial cells (Pena et al., 2000). This is mediated by the lipid second messenger ceramide via activation of acid sphingomyelinase (ASM) (Pena et al., 2000). The extent of apoptosis is significantly reduced by the intravenous administration of bFGF treatment, which suggests that this is one mechanism for preventing irradiation-induced loss of vascular endothelium (Pena et al., 2000). For rat RGCs, neuroprotection against irradiation-induced glutamate induced apoptotic signaling following irradiation is provided by inhibiting the NMDA receptor glycine subunit (Qiu et al., 2010).

Is there an optimal approach?

Each of the above described methods reduces irradiation-induced neurotoxicity, with some having greater clinical applicability than others, but with NSAIDs presently appearing to provide the greatest degree of neuroprotection. For the other techniques, the limitation to their clinical use lies in the insufficient extent to which singly they reduce inflammation and its consequences, and whether they can be used without causing global problems by disrupting the function of healthy neurons. In addition, further studies are required to examine whether these techniques can be used in combination to provide enhanced neuroprotection.

Please cite this article as: Kuffler, D.P., Hyperbaric oxygen therapy: Can it prevent irradiation-induced necrosis? Exp. Neurol. (2012), doi:10.1016/j.expneurol.2012.03.011

HBOT for reducing irradiation-induced inflammation and neurotoxicity

HBOT is indicated for patients as soon as they manifest irradiation-induced inflammation and necrosis, because it reduces or retards further development of irradiation side effects (Nazario and Kuffler, 2011). HBOT acts to reduce cerebral edema, normalize water content in the brain, decrease the severity of brain infarction, maintains blood–brain barrier integrity, promotes antioxidant defenses, suppresses the proliferation of macrophages and foam cells, and prevents activated macrophages and astrocytes from releasing neurotoxic factors, thereby resulting in improved clinical outcomes and neuronal survival, and accelerates the resolution of clinical symptoms following irradiation treatment (Al-Waili et al., 2005a, 2005b; Wasilewska et al., 2011). HBOT leads to an improvement and/or stabilization of neurological symptoms of patients (Chuba et al., 1997; Cihan et al., 2009; Kohshi et al., 2003). Since HBOT manifests no adverse clinical influences, its application following irradiation, but before the manifestation of neurological side effects may help avert the development of both early and delayed onset inflammation and necrosis (Tumerdem-Ulug et al., 2011). Following is a discussion of some mechanisms by which HBOT provides neuroprotection against acute irradiation-induced inflammation and necrosis.

Inflammatory cell infiltration

Matrix metalloproteinases (MMPs), especially MMP-9, promote the transmigration of activated human renal cell carcinoma neutrophils, (Kim et al., 2004) which in mice are the main source of MMPs (Albaiceta et al., 2008). For the rat, HBOT significantly decreases neuron death, neutrophilic inflammatory infiltration and their expression of MMPs, which should provide neuroprotection (Vlodavsky et al., 2006).

Clinically, HBOT also reduces irradiation-induced neurotoxicity by preventing irradiation-induced recruitment and activation of macrophages and astrocytes, and blocking microglia loss of calcium homeostasis (Bennett et al., 2005; Eyupoglu et al., 2003; Feldmeier, 2004a, 2004b; Gunther et al., 2005; Morabito et al., 2011), and preventing the synthesis of PGE2 and Cox-2 mRNA, (Al-Waili and Butler, 2006) and both in mice and in vitro, the release of proinflammatory neurotoxic cytokines and BDNF, while significantly increasing levels of VEGF and other growth factors, which reduces vascular permeability and induces angiogenesis in a dose- and time-dependent manner (Hayakawa et al., 1997; Kudchodkar et al., 2008; Lee et al., 2006a, 2006b).

Stabilizing microglia calcium homeostasis thereby reducing synthesis of neurotoxic cytokines, neurotrophic factors and NO

As stated, irradiation induces neurotoxic inflammation and oxidative stress by inducing macrophage and microglia recruitment and activation and loss of calcium homeostasis, which result in their synthesis and release of neurotoxic inflammatory cytokines (Mizoguchi et al., 2011). Clinically, HBOT provides neuroprotection by inducing anti-inflammatory activity by blocking the release proinflammatory cytokines, PGs, Cox-2, iNOS and NO activities (Ercin et al., 2009; Granowitz et al., 2002; Kendall et al., 2012), by suppressing interferon-gamma (IFN-gamma) release, (Granowitz et al., 2002) and in rats significantly upregulating the production of neuroprotective VEGF (Sumen et al., 2001). This may in part result from causing a decrease in intracellular calcium that is required for the release of cytokines by astroglia.

In rats, glial cell line-derived neurotrophic factor (GDNF) is present in infiltrating inflammatory cells including macrophages and T cells (Ahn et al., 2010). In mice, GDNF restores epithelial barrier function by reducing increased epithelial permeability and inhibiting mucosal inflammatory response (Zhang et al., 2010). Although HBOT does not change the extent of macrophage proliferation or microglia activation, it significantly reduces the gene expression of GDNF and inducible iNOS. Thus, HBOT may suppress apoptosis, by inhibiting the iNOS gene (Yu et al., 2004).

Toll-like receptors (TLRs) are key components in the innate immune responses and their signaling pathway activates genes such as nuclear factor-kappaB (NF-kappaB) and cytokines involved in inflammation and immune responses. In rats, HBOT significantly reduces the expression of TLR2 and TLR4, NF-kappaB activation, and cytokine production, and thus the severity of tissue inflammation and damage (Rinaldi et al., 2011).

HBOT provides an anti-inflammatory action in mice and rats by increasing the production of hepatocyte growth factor (HGF) and basic fibroblast growth factor (bFGF) (Asano et al., 2007; Gong et al., 2004).

Irradiation-induced inflammation is associated with the increased production of TNF-alpha, which causes neurotoxicity (Li et al., 2011). HBOT significantly reduces the tissue TNF-alpha (Li et al., 2011), suggesting that HBOT prevents the inflammation-induced neurotoxicity caused by TNF-alpha production.

Reducing the toxicity of oxygen-derived free radicals

Irradiation induces oxidative stress mediated by the generation of oxygen-derived free radicals, which leads to peroxidation of unsaturated fatty acids in cell membranes, (Yoshida et al., 2006) which damages vascular endothelial function, leading to acute or chronic inflammation (Yamashita et al., 2006). HBOT reduces the toxicity of oxygen-derived free radicals (Yamashita et al., 2006). In rats, neuroprotection against inflammation and oxidative stress can also be achieved by decreasing the levels of proinflammatory factors, such as tumor TNF-alpha, interleukin-1beta (IL-1beta), interleukin-6 (IL-6), inducible iNOS, and cyclooxygenase-2 (COX-2) (Moon et al., 2012). In PC-12 cells and zebrafish, flavonoids, potent antioxidants, provide neuroprotection against oxidative stress and apoptosis by inhibiting NO over-production, iNOS over-expression, and down-regulating the over-expression of pro-inflammatory genes for IL-1ss, TNF-alpha and COX-2 (Zhang et al., 2011). For cultured rat neurons, the free radical scavenger edaravone provides neuroprotection against glutamate neurotoxicity (Hisano et al., 2009).

Altering gene expression

Clinically, HBOT causes the down-regulation of 19 genes involved in inflammation and oxidative stress (Cobo Plana et al., 2000), which prevents them from suffering irradiation induced neurotoxicity (Kendall et al., 2012). Simultaneously, HBOT leads to a decrease in the expression of endothelial IL-8 mRNA and its protein, leading to the alleviation of the inflammatory processes. Because this influence is transitory, it is recommended that HBOT be provided on a daily basis (Kendall et al., 2012).

Induction of angiogenesis

While the maintenance of healthy tissue requires an intact vasculature, therapeutic irradiation causes neurotoxic influences by triggering progressive and irreversible vasculature damage in the rat (Sminia et al., 2003a, 2003b; Teguh et al., 2009a, 2009b). HBOT can provide neuroprotection by triggering the expression of visfatin, an adipocytokine with insulin-mimetic effect, (Wang et al., 2011) and angiopoietin-2 (Ang2) (Lin et al., 2002), which induces endothelial angiogenesis in humans and prevents irradiation-induced tissue pathology (Doida et al., 1992).

Clinically and for rats, HBOT administered shortly after irradiation induces angiogenesis in healthy tissue, and reduces late irradiation injury when applied during the latent period before complications become manifest (Feldmeier et al., 1995; Sminia et al., 2003a, 2003b; Teguh et al., 2009a, 2009b). Clinically, HBOT leads to the upregulated expression of the angiogenin gene, which stimulates angiogenesis and increases the

Please cite this article as: Kuffler, D.P., Hyperbaric oxygen therapy: Can it prevent irradiation-induced necrosis? Exp. Neurol. (2012), doi:10.1016/j.expneurol.2012.03.011

concentration of antioxidant enzymes, and inhibits various irradiation-triggered cascades that trigger inflammation and neurotoxicity (Kendall et al., 2012). This leads to a decrease in endothelial IL-8 mRNA and protein, which helps alleviate inflammatory processes (Kendall et al., 2012). These functions are essential for preserving neuron viability by maintaining tissue oxygenation (Cobo Plana et al., 2000). The transient influence of HBOT indicates that HBOT must be provided on a daily basis.

Reducing CNS inflammation

In clinical studies, HBOT pretreatment reduces the ischemia-induced inflammatory responses of the CNS, (Alex et al., 2005) possibly by upregulating the expression of angiogenin gene, which promotes angiogenesis, while simultaneously down-regulating genes involved in inflammation (Kendall et al., 2012). Thus, the application of HBOT immediately following irradiation may prevent irradiation-induced inflammation.

Blocking apoptosis

Cranial irradiation leads to neurotoxicity by triggering apoptotic signaling. In rat pups, HBOT preconditioning provides protection against hypoxic ischemia by inhibiting the neuronal apoptosis pathway (Li et al., 2008). Activation of Rho in animal cells in vitro induces apoptosis while suppression of Rho activation inhibits the apoptosis pathway (Koyanagi et al., 2008). For human cells, chemical hypoxia promotes inducible iNOS gene expression, lipid peroxidation, leukotriene B(4) generation and apoptosis, while inhibition of iNOS reduces apoptosis of human cells in vitro (Kiang et al., 2008).

Duration of HBOT

A relatively standard and effective HBOT regime consists of 30–40 sessions, with 1–2 sessions daily, at 2.5 ATA with oxygen breathing for 90 min daily, 5–7 days per week, applied shortly after irradiation, although some evidence suggests that 60–90 sessions are more successful (Hampson and Corman, 2007a, 2007b; Harding et al., 2008; Perez-Espejo et al., 2009; Teguh et al., 2009a, 2009b; Williamson, 2007). While fewer HBOT sessions provide less protection, the time over which the HBOT is given (3 vs. 7 weeks) does not influence the clinical effectiveness of the HBOT (Hampson and Corman, 2007a, 2007b; Levy and Miller, 2006). Finally, it appears that the total number of HBOT sessions is more critical to neurological protection than the time distribution of their application.

Performing a clinical study

To determine whether neurological side effects are due to irradiation-induced inflammation of the irradiated and surrounding tissue several questions must be addressed. First, are the development, severity and duration of inflammation associated directly with the appearance, development and disappearance of the dark line surrounding irradiated tissue, indicating inflammation in T2 weighted MR images of irradiated tissue? Second, does the duration and disappearance of inflammation parallel the severity and disappearance of neurological side effects? And third, does a delay in the appearance, magnitude and duration of irradiation result in a delay in the onset, magnitude and duration of inflammation, and therefore the severity and duration of neurological side effects?

Most studies examining the influences of HBOT and different factors that induce or inhibit inflammation and the actions of neurotoxic cytokines have been performed on animal models and cells in vitro. There only limited experimental and clinical data on the mechanisms by which HBOT effects these actions (Spiegelberg et al., 2010). Therefore, one can only hypothesize whether what has been observed in these models parallels those that would take place clinically. This means that further clinical studies are required to determine the mechanisms of actions of HBOT alone or in combination with other techniques on the reduction and elimination of irradiation-induced inflammation and neurological side effects.

Contraindications for HBOT

Although HBOT is generally well tolerated, there are a number of conditions under which HBOT is contraindicated. Some of these include untreated pneumothorax (a condition in which is an abnormal collection of air or gas in the pleural space that separates the lung from the chest wall, and that may interfere with normal breathing), and when patients are on certain drugs, such as Bleomycin, Cisplatin, Disulfiram, and Sulfamylon. Other contraindications include patients with asthma, claustrophobia, chronic obstructive pulmonary disease, eustachian tube dysfunction, pregnancy, seizures and upper respiratory infection (Bennett et al., 2008).

New perspectives

Clinically NSDIs are presently indicated to ameliorate the delayed side effects of irradiation only after they become manifest (Feldmeier, 2004a, 2004b). However, as mentioned above, a number of different techniques reduce inflammation, but are currently only used singly and not in combinations. Therefore, studies are required to determine which combination/s may provide greater neuroprotection than any one alone. Until then, NSAIDs should be administered as soon as irradiation-induced necrosis becomes apparent. However, as soon as it is apparent that NSAIDs are not effective, HBOT should be immediately initiated. But, when HBOT is started, the administration of NSAIDs should be continued because their combined actions may provide even greater efficacy in reducing inflammation and reducing irradiation-induced neurological side effects than any approach singly.

Clinical and animal model studies indicate that HBOT provides protection against irradiation-induced inflammation and necrosis by up-regulating the expression of angiogenin gene expression, which promotes angiogenesis, while simultaneously down-regulating genes involved in inflammation, (Alex et al., 2005; Kendall et al., 2012). Therefore, it is reasonable to assume that the administration of HBOT within days to months after irradiation, but before rather than after the manifestation of irradiation-induced inflammation and necrosis, would prevent the severity of irradiation-induced inflammation and necrosis or their severity. Clinical studies are required to determine whether the administration of HBOT within weeks to months after irradiation, alone or in combination with the other techniques described above, provides greater neuroprotection than when applied only after the manifestation of neurological side effects.

In a study on rats that underwent spinal cord irradiation, no significant differences were seen in the appearance of neurological complications if the animals underwent irradiation alone compared to irradiation combined with HBOT administered from 5 to 15 weeks post irradiation (Sminia et al., 2003a, 2003b). However, in a clinical study, patients who underwent HBOT shortly after receiving irradiation suffered less severe neurological side effects and had better quality of life compared to control patients who did not undergo HBOT (Teguh et al., 2009a, 2009b). One explanation for these differences is differences between on rats and humans. Another is that the outcomes differed because different tissues were irradiated. Further studies are required to determine whether the outcomes of animal studies of relevant to clinical outcomes. To this aim it will be critical to minimize the source of differences that may arise from irradiating different tissues, the volume of tissue irradiated, and the irradiation doses used. However, the clinical finding that HBOT is effective in preventing or reducing irradiation-induced neurological side when used before the irradiation-induced side effects become manifest is very promising for future clinical studies.

Since there is no convincing clinical evidence that HBOT enhances or stimulates malignant growth or neurological side effects, (Hampson

Please cite this article as: Kuffler, D.P., Hyperbaric oxygen therapy: Can it prevent irradiation-induced necrosis? Exp. Neurol. (2012), doi:10.1016/j.expneurol.2012.03.011

and Corman, 2007a, 2007b; Safra et al., 2008) and that HBOT does not increase tissue irradiation tolerance, (Sminia et al., 2003a, 2003b) initiating HBOT before the manifestation of necrosis should not be a clinical concern. However, it is clear that the use of HBOT is expensive, time consuming and inconvenient for the patient. Further, it can be argued that such use of HBOT is not reasonable because it is impossible to anticipate which patients may manifest delayed irradiation-induced necrosis, which means patients would be treated with HBOT who would not manifest necrosis. This argument leads to the recommendation that it is important to attempt to determine which patients are most likely predisposed to develop delayed irradiation-induced tissue necrosis, which would allow HBOT to be administered only to those patients with a likelihood of developing tissue necrosis.

Perhaps the strongest argument for initiating HBOT before the appearance of irradiation-induced necrosis is the clinical outcome where the irradiated target tissue is the optic nerve or adjacent tissue. Such patients can suffer irradiation-induced deterioration of vision, (Arvold et al., 2009) but HBOT can prevent permanent vision loss, only if it is initiated as soon as possible after the onset of the vision loss is identified (Levy and Miller, 2006).

Conclusions

Neurological complications caused by irradiation result from progressive and irreversible vascular damage and resulting inflammation. Upon manifestation of irradiation-induced necrosis, patients should immediately be treated with NSAIDs, and if they are not effective HBOT should be initiated because it results in the down-regulation of inflammation inducing genes and induces angiogenesis within irradiated tissue. HBOT can thereby reduce the further development of late irradiation injury. However, clinical data suggest that it would be better for patients to undergo HBOT before rather than after the manifestation of irradiation-induced inflammation and necrosis. Further studies are required to determine when following irradiation is HBOT most effective in reducing or preventing irradiation-induced necrosis. The preponderance of data indicates that the total number of HBOT sessions is more critical than the time distribution of their application, with a minimum of 30 sessions, but 60–90 sessions being more successful, but further studies are required to determine the optimal number of sessions to use. Finally, although a number of drug therapies reduce the deleterious side effects of cranial irradiation, with NSAIDs being the most effective, further studies are required to determine whether combining some of these techniques would be more effective than using NSAIDs alone. In conclusion, while the body of published data support the conclusion that HBOT is the most effective technique for improving the outcome of patients suffering delayed irradiation-induced brain necrosis of the brain, evidence suggests that HBOT may be more successful if its application was changed from after the manifestation of necrosis occur to before, and that neuroprotection may be further improved by combining HBOT with a combination of drug therapies.

Acknowledgments

No conflicts of interest were involved in this paper.

References

Abbott, N.J., 2000. Inflammatory mediators and modulation of blood–brain barrier permeability. Cell. Mol. Neurobiol. 20, 131–147.
Achanta, P., Thompson, K.J., Fuss, M., Martinez Jr., J.L., 2007. Gene expression changes in the rodent hippocampus following whole brain irradiation. Neurosci. Lett. 418, 143–148.
Adamson, I.Y., Bowden, D.H., 1983. Endothelial injury and repair in radiation-induced pulmonary fibrosis. Am. J. Pathol. 112, 224–230.
Ahn, M., Jin, J.K., Moon, C., Matsumoto, Y., Koh, C.S., Shin, T., 2010. Glial cell line-derived neurotrophic factor is expressed by inflammatory cells in the sciatic nerves of Lewis rats with experimental autoimmune neuritis. J. Peripher. Nerv. Syst. : JPNS 15, 104–112.
Ajami, B., Bennett, J.L., Krieger, C., McNagny, K.M., Rossi, F.M., 2011. Infiltrating monocytes trigger EAE progression, but do not contribute to the resident microglia pool. Nat. Neurosci. 14, 1142–1149.
Akamatsu, Y., Murakami, K., Watanabe, M., Jokura, H., Tominaga, T., 2010. Malignant peripheral nerve sheath tumor arising from benign vestibular schwannoma treated by gamma knife radiosurgery after two previous surgeries: a case report with surgical and pathological observations. World Neurosurg. 73, 751–754.
Albaiceta, G.M., Gutierrez-Fernandez, A., Parra, D., Astudillo, A., Garcia-Prieto, E., Taboada, F., Fueyo, A., 2008. Lack of matrix metalloproteinase-9 worsens ventilator-induced lung injury. Am. J. Physiol. Lung Cell. Mol. Physiol. 294, L535–L543.
Alex, J., Laden, G., Cale, A.R., Bennett, S., Flowers, K., Madden, L., Gardiner, E., McCollum, P.T., Griffin, S.C., 2005. Pretreatment with hyperbaric oxygen and its effect on neuropsychometric dysfunction and systemic inflammatory response after cardiopulmonary bypass: a prospective randomized double-blind trial. J. Thorac. Cardiovasc. Surg. 130, 1623–1630.
Al-Waili, N.S., Butler, G.J., 2006. Effects of hyperbaric oxygen on inflammatory response to wound and trauma: possible mechanism of action. Sci. World J. 6, 425–441.
Al-Waili, N.S., Butler, G.J., Beale, J., Abdullah, M.S., Hamilton, R.W., Lee, B.Y., Lucus, P., Allen, M.W., Petrillo, R.L., Carrey, Z., Finkelstein, M., 2005a. Hyperbaric oxygen in the treatment of patients with cerebral stroke, brain trauma, and neurologic disease. Adv. Ther. 22, 659–678.
Al-Waili, N.S., Butler, G.J., Beale, J., Hamilton, R.W., Lee, B.Y., Lucas, P., 2005b. Hyperbaric oxygen and malignancies: a potential role in radiotherapy, chemotherapy, tumor surgery and phototherapy. Med. Sci. Monit. 11 RA279-289..
Anscher, M.S., Vujaskovic, Z., 2005. Mechanisms and potential targets for prevention and treatment of normal tissue injury after radiation therapy. Semin. Oncol. 32, S86–S91.
Arvold, N.D., Lessell, S., Bussiere, M., Beaudette, K., Rizzo, J.F., Loeffler, J.S., Shih, H.A., 2009. Visual outcome and tumor control after conformal radiotherapy for patients with optic nerve sheath meningioma. Int. J. Radiat. Oncol. Biol. Phys. 75, 1166–1172.
Asano, T., Kaneko, E., Shinozaki, S., Imai, Y., Shibayama, M., Chiba, T., Ai, M., Kawakami, A., Asaoka, H., Nakayama, T., Mano, Y., Shimokado, K., 2007. Hyperbaric oxygen induces basic fibroblast growth factor and hepatocyte growth factor expression, and enhances blood perfusion and muscle regeneration in mouse ischemic hind limbs. Circ. J. : Off. J. Jpn. Circ. Soc. 71, 405–411.
Ben Abdallah, N.M., Slomianka, L., Lipp, H.P., 2007. Reversible effect of X-irradiation on proliferation, neurogenesis, and cell death in the dentate gyrus of adult mice. Hippocampus 17, 1230–1240.
Bennett, M.H., Feldmeier, J., Hampson, N., Smee, R., Milross, C., 2005. Hyperbaric oxygen therapy for late radiation tissue injury. Cochrane Database Syst. Rev. CD005005.
Bennett, M., Feldmeier, J., Smee, R., Milross, C., 2008. Hyperbaric oxygenation for tumour sensitisation to radiotherapy: a systematic review of randomised controlled trials. Cancer Treat. Rev. 34, 577–591.
Bills, V.L., Salmon, A.H., Harper, S.J., Overton, T.G., Neal, C.R., Jeffery, B., Soothill, P.W., Bates, D.O., 2011. Impaired vascular permeability regulation caused by the VEGFb splice variant in pre-eclampsia. BJOG 118, 1253–1261.
Blomstrand, C., Johansson, B., Rosengren, B., 1975. Dexamethasone effect on blood–brain barrier damage caused by acute hypertension in x-irradiated rabbits. Acta Neurol. Scand. 52, 331–334.
Butler, J.M., Rapp, S.R., Shaw, E.G., 2006. Managing the cognitive effects of brain tumor radiation therapy. Curr. Treat. Options Oncol. 7, 517–523.
Celix, J.M., Douglas, J.G., Haynor, D., Goodkin, R., 2009. Thrombosis and hemorrhage in the acute period following Gamma Knife surgery for arteriovenous malformation. Case Rep. J. Neurosurg. 111, 124–131.
Chan, Y.L., Yeung, D.K., Leung, S.F., Chan, P.N., 2003. Diffusion-weighted magnetic resonance imaging in radiation-induced cerebral necrosis. Apparent diffusion coefficient in lesion components. J. Comput. Assist. Tomogr. 27, 674–680.
Chang, Y.H., Chen, P.L., Tai, M.C., Chen, C.H., Lu, D.W., Chen, J.T., 2006. Hyperbaric oxygen therapy ameliorates the blood–retinal barrier breakdown in diabetic retinopathy. Clin. Experiment. Ophthalmol. 34, 584–589.
Chiang, C.S., McBride, W.H., Withers, H.R., 1993. Radiation-induced astrocytic and microglial responses in mouse brain. Radiother. Oncol : J Eur. Soc. Ther. Radiol. Oncol. 29, 60–68.
Chin, L.S., Lazio, B.E., Biggins, T., Amin, P., 2000. Acute complications following gamma knife radiosurgery are rare. Surg. Neurol. 53, 498–502 discussion 502..
Chuba, P.J., Aronin, P., Bhambhani, K., Eichenhorn, M., Zamarano, L., Cianci, P., Muhlbauer, M., Porter, A.T., Fontanesi, J., 1997. Hyperbaric oxygen therapy for radiation-induced brain injury in children. Cancer 80, 2005–2012.
Cicciarello, R., d'Avella, D., Gagliardi, M.E., Albiero, F., Vega, J., Angileri, F.F., D'Aquino, A., Tomasello, F., 1996. Time-related ultrastructural changes in an experimental model of whole brain irradiation. Neurosurgery 38, 772–779 discussion 779–780..
Cihan, Y.B., Uzun, G., Yildiz, S., Donmez, H., 2009. Hyperbaric oxygen therapy for radiation-induced brain necrosis in a patient with primary central nervous system lymphoma. J. Surg. Oncol. 100, 732–735.
Clavo, B., Robaina, F., Montz, R., Carames, M.A., Lloret, M., Ponce, P., Hernandez, M.A., Carreras, J.L., 2009. Modification of glucose metabolism in radiation-induced brain injury areas using cervical spinal cord stimulation. Acta Neurochir. 151, 1419–1425.
Cobo Plana, J., Diaz Villa, B., de Carlos Villafranca, F., Diaz Esnal, L., 2000. Remission of nocturnal enuresis in three patients with orthodontic advance mandibular appliance. An. Esp. Pediatr. 52, 201–202.
Covo, S., Westmoreland, J.W., Reddy, A.K., Gordenin, D.A., Resnick, M.A., 2012. RAD53 is limiting in double-strand break repair and in protection against toxicity associated with ribonucleotide reductase inhibition. DNA Repair (Amst) 11, 317–323.
d'Avella, D., Cicciarello, R., Angileri, F.F., Lucerna, S., La Torre, D., Tomasello, F., 1998. Radiation-induced blood–brain barrier changes: pathophysiological mechanisms and clinical implications. Acta Neurochir. Suppl. 71, 282–284.

Please cite this article as: Kuffler, D.P., Hyperbaric oxygen therapy: Can it prevent irradiation-induced necrosis? Exp. Neurol. (2012), doi:10.1016/j.expneurol.2012.03.011

Dea, N., Borduas, M., Kenny, B., Fortin, D., Mathieu, D., 2010. Safety and efficacy of Gamma Knife surgery for brain metastases in eloquent locations. J. Neurosurg. 113 (Suppl.), 79–83.
Delanian, S., Lefaix, J.L., 2004. The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. Radiother. Oncol. : J. Eur. Soc. Ther. Radiol. Oncol. 73, 119–131.
Delanian, S., Lefaix, J.L., 2007. Current management for late normal tissue injury: radiation-induced fibrosis and necrosis. Semin. Radiat. Oncol. 17, 99–107.
Djalilian, H.R., Benson, A.G., Ziai, K., Safai, Y., Thakkar, K.H., Mafee, M.F., 2007. Radiation necrosis of the brain after radiosurgery for vestibular schwannoma. Am. J. Otolaryngol. 28, 338–341.
Doida, Y., Brayman, A.A., Miller, M.W., 1992. Modest enhancement of ultrasound-induced mutations in V79 cells in vitro. Ultrasound Med. Biol. 18, 465–469.
Dong, X., Dong, J., Zhang, R., Fan, L., Liu, L., Wu, G., 2009. Anti-inflammatory effects of tanshinone IIA on radiation-induced microglia BV-2 cells inflammatory response. Cancer Biother. Radiopharm. 24, 681–687.
Drew, P.D., Chavis, J.A., 2000. Inhibition of microglial cell activation by cortisol. Brain Res. Bull. 52, 391–396.
Eberhardt, J.L., Persson, B.R., Brun, A.E., Salford, L.G., Malmgren, L.O., 2008. Blood–brain barrier permeability and nerve cell damage in rat brain 14 and 28 days after exposure to microwaves from GSM mobile phones. Electromagn. Biol. Med. 27, 215–229.
Ercin, C.N., Yesilova, Z., Korkmaz, A., Ozcan, A., Oktenli, C., Uygun, A., 2009. The effect of iNOS inhibitors and hyperbaric oxygen treatment in a rat model of experimental colitis. Dig. Dis. Sci. 54, 75–79.
Eyupoglu, I.Y., Bechmann, I., Nitsch, R., 2003. Modification of microglia function protects from lesion-induced neuronal alterations and promotes sprouting in the hippocampus. FASEB J. : Off publ. Fed. Am. Soc. Exp. Biol. 17, 1110–1111.
Farber, K., Kettenmann, H., 2006. Functional role of calcium signals for microglial function. Glia 54, 656–665.
Feldmeier, J.J., 2004a. Hyperbaric oxygen for delayed radiation injuries. Undersea Hyperb. Med. 31, 133–145.
Feldmeier, J.J., 2004b. Hyperbaric oxygen for delayed radiation injuries. Undersea Hyperb. Med. 31, 133–145.
Feldmeier, J.J., Heimbach, R.D., Davolt, D.A., Court, W.S., Stegmann, B.J., Sheffield, P.J., 1995. Hyperbaric oxygen as an adjunctive treatment for delayed radiation injury of the chest wall: a retrospective review of twenty-three cases. Undersea Hyperb. Med. 22, 383–393.
Fischer, S., Clauss, M., Wiesnet, M., Renz, D., Schaper, W., Karliczek, G.F., 1999. Hypoxia induces permeability in brain microvessel endothelial cells via VEGF and NO. Am. J. Physiol. 276, C812–C820.
Flanders, K.C., Sullivan, C.D., Fujii, M., Sowers, A., Anzano, M.A., Arabshahi, A., Major, C., Deng, C., Russo, A., Mitchell, J.B., Roberts, A.B., 2002. Mice lacking Smad3 are protected against cutaneous injury induced by ionizing radiation. Am. J. Pathol. 160, 1057–1068.
Foroughi, M., Kemeny, A.A., Lehecka, M., Wons, J., Kajdi, L., Hatfield, R., Marks, S., 2010. Operative intervention for delayed symptomatic radionecrotic masses developing following stereotactic radiosurgery for cerebral arteriovenous malformations—case analysis and literature review. Acta Neurochir. 152, 803–815.
Geraci, J.P., Mariano, M.S., Jackson, K.L., 1993. Amelioration of radiation nephropathy in rats by dexamethasone treatment after irradiation. Radiat. Res. 134, 86–93.
Ghardi, M., Moreels, M., Chatelain, B., Chatelain, C., Baatout, S., in press. Radiation-induced double strand breaks and subsequent apoptotic DNA. Int. J. Mol. Med.
Gong, R., Rifai, A., Tolbert, E.M., Biswas, P., Centracchio, J.N., Dworkin, L.D., 2004. Hepatocyte growth factor ameliorates renal interstitial inflammation in rat remnant kidney by modulating tubular expression of macrophage chemoattractant protein-1 and RANTES. J. Am. Soc. Nephrol. : JASN 15, 2868–2881.
Gonzalez-Velasquez, F.J., Reed, J.W., Fuseler, J.W., Matherly, E.E., Kotarek, J.A., Soto-Ortega, D.D., Moss, M.A., 2011. Activation of brain endothelium by soluble aggregates of the amyloid-beta protein involves nuclear factor-kappaB. Curr. Alzheimer Res. 8, 81–94.
Granowitz, E.V., Skulsky, E.J., Benson, R.M., Wright, J., Garb, J.L., Cohen, E.R., Smithline, E.C., Brown, R.B., 2002. Exposure to increased pressure or hyperbaric oxygen suppresses interferon-gamma secretion in whole blood cultures of healthy humans. Undersea Hyperb. Med. : J. Undersea Hyperb. Med. Soc. Inc 29, 216–225.
Griem, M.L., Robotewskyj, A., Nagel, R.H., 1994. Potential vascular damage from radiation in the space environment. Adv. Space Res. 14, 555–563.
Grombacher, T., Mitra, S., Kaina, B., 1996. Induction of the alkyltransferase (MGMT) gene by DNA damaging agents and the glucocorticoid dexamethasone and comparison with the response of base excision repair genes. Carcinogenesis 17, 2329–2336.
Gronier, S., Bourg, V., Frenay, M., Cohen, M., Mondot, L., Thomas, P., Lebrun, C., 2011. Bevacizumab for the treatment of cerebral radionecrosis. Rev. Neurol. 167, 331–336.
Gunther, A., Kuppers-Tiedt, L., Schneider, P.M., Kunert, I., Berrouschot, J., Schneider, D., Rossner, S., 2005. Reduced infarct volume and differential effects on glial cell activation after hyperbaric oxygen treatment in rat permanent focal cerebral ischaemia. Eur. J. Neurosci. 21, 3189–3194.
Haagen, J., Krohn, H., Rollig, S., Schmidt, M., Wolfram, K., Dorr, W., 2009. Effect of selective inhibitors of inflammation on oral mucositis: preclinical studies. Radiother. Oncol. : J. Eur. Soc. Ther. Radiol. Oncol. 92, 472–476.
Hampson, N.B., Corman, J.M., 2007a. Rate of delivery of hyperbaric oxygen treatments does not affect response in soft tissue radionecrosis. Undersea Hyperb. Med. 34, 329–334.
Hampson, N.B., Corman, J.M., 2007b. Rate of delivery of hyperbaric oxygen treatments does not affect response in soft tissue radionecrosis. Undersea Hyperb. Med. 34, 329–334.
Harding, S.A., Hodder, S.C., Courtney, D.J., Bryson, P.J., 2008. Impact of perioperative hyperbaric oxygen therapy on the quality of life of maxillofacial patients who undergo surgery in irradiated fields. Int. J. Oral Maxillofac. Surg. 37, 617–624.
Hayakawa, K., Borchardt, P.E., Sakuma, S., Ijichi, A., Niibe, H., Tofilon, P.J., 1997. Microglial cytokine gene induction after irradiation is affected by morphologic differentiation. Radiat. Med. 15, 405–410.
Hirano, M., Shibato, J., Rakwal, R., Kouyama, N., Katayama, Y., Hayashi, M., Masuo, Y., 2009. Transcriptomic analysis of rat brain tissue following gamma knife surgery: early and distinct bilateral effects in the un-irradiated striatum. Mol. Cells 27, 263–268.
Hisano, K., Watanabe, M., Morimoto, Y., 2009. Protective effects of the free radical scavenger edaravone against glutamate neurotoxicity in nearly pure neuronal culture. J. Anesth. 23, 363–369.
Hwang, S.Y., Jung, J.S., Kim, T.H., Lim, S.J., Oh, E.S., Kim, J.Y., Ji, K.A., Joe, E.H., Cho, K.H., Han, I.O., 2006. Ionizing radiation induces astrocyte gliosis through microglia activation. Neurobiol. Dis. 21, 457–467.
Hwang, J., Zheng, L.T., Ock, J., Lee, M.G., Kim, S.H., Lee, H.W., Lee, W.H., Park, H.C., Suk, K., 2008. Inhibition of glial inflammatory activation and neurotoxicity by tricyclic antidepressants. Neuropharmacology 55, 826–834.
Johnston, C.J., Williams, J.P., Elder, A., Hernady, E., Finkelstein, J.N., 2004. Inflammatory cell recruitment following thoracic irradiation. Exp. Lung Res. 30, 369–382.
Kabacik, S., Mackay, A., Tamber, N., Manning, G., Finnon, P., Paillier, F., Ashworth, A., Bouffler, S., Badie, C., 2011. Gene expression following ionising radiation: identification of biomarkers for dose estimation and prediction of individual response. Int. J. Radiat. Biol. 87, 115–129.
Kalm, M., Lannering, B., Bjork-Eriksson, T., Blomgren, K., 2009. Irradiation-induced loss of microglia in the young brain. J. Neuroimmunol. 206, 70–75.
Kargiotis, O., Geka, A., Rao, J.S., Kyritsis, A.P., 2010. Effects of irradiation on tumor cell survival, invasion and angiogenesis. J. Neurooncol 100, 323–338.
Kawasaki, A., Han, M.H., Wei, J.Y., Hirata, K., Otori, Y., Barnstable, C.J., 2002. Protective effect of arachidonic acid on glutamate neurotoxicity in rat retinal ganglion cells. Invest. Ophthalmol. Vis. Sci. 43, 1835–1842.
Kendall, A.C., Whatmore, J.L., Harries, L.W., Winyard, P.G., Smerdon, G.R., Eggleton, P., 2012. Changes in inflammatory gene expression induced by hyperbaric oxygen treatment in human endothelial cells under chronic wound conditions. Exp. Cell Res. 318, 207–216.
Kiang, J.G., Krishnan, S., Lu, X., Li, Y., 2008. Inhibition of inducible nitric-oxide synthase protects human T cells from hypoxia-induced apoptosis. Mol. Pharmacol. 73, 738–747.
Kim, J.H., Lee, S.Y., Bak, S.M., Suh, I.B., Shin, C., Shim, J.J., In, K.H., Kang, K.H., Yoo, S.H., 2004. Effects of matrix metalloproteinase inhibitor on LPS-induced goblet cell metaplasia. Am. J. Physiol. Lung Cell. Mol. Physiol. 287, L127–L133.
Kohshi, K., Imada, H., Nomoto, S., Yamaguchi, R., Abe, H., Yamamoto, H., 2003. Successful treatment of radiation-induced brain necrosis by hyperbaric oxygen therapy. J. Neurol. Sci. 209, 115–117.
Kosower, N.S., Newton, G.L., Kosower, E.M., Ranney, H.M., 1980. Bimane fluorescent labels. Characterization of the bimane labeling of human hemoglobin. Biochim. Biophys. Acta 622, 201–209.
Koyanagi, M., Takahashi, J., Arakawa, Y., Doi, D., Fukuda, H., Hayashi, H., Narumiya, S., Hashimoto, N., 2008. Inhibition of the Rho/ROCK pathway reduces apoptosis during transplantation of embryonic stem cell-derived neural precursors. J. Neurosci. Res. 86, 270–280.
Kudchodkar, B., Jones, H., Simecka, J., Dory, L., 2008. Hyperbaric oxygen treatment attenuates the pro-inflammatory and immune responses in apolipoprotein E knockout mice. Clin. Immunol. 128, 435–441.
Lee, T.K., Stupans, I., 2002. Radioprotection: the non-steroidal anti-inflammatory drugs (NSAIDs) and prostaglandins. J. Pharm. Pharmacol. 54, 1435–1445.
Lee, C.C., Chen, S.C., Tsai, S.C., Wang, B.W., Liu, Y.C., Lee, H.M., Shyu, K.G., 2006a. Hyperbaric oxygen induces VEGF expression through ERK, JNK and c-Jun/AP-1 activation in human umbilical vein endothelial cells. J. Biomed. Sci. 13, 143–156.
Lee, K.S., Park, H.S., Park, S.J., Kim, S.R., Min, K.H., Jin, S.M., Li, L., Lee, Y.C., 2006b. An antioxidant modulates expression of receptor activator of NF-kappaB in asthma. Exp. Mol. Med. 38, 217–229.
Lee, W.H., Sonntag, W.E., Mitschelen, M., Yan, H., Lee, Y.W., 2010. Irradiation induces regionally specific alterations in pro-inflammatory environments in rat brain. Int. J. Radiat. Biol. 86, 132–144.
Lee, M., Suk, K., Kang, Y., McGeer, E., McGeer, P.L., 2011. Neurotoxic factors released by stimulated human monocytes and THP-1 cells. Brain Res. 1400, 99–111.
Lesser, R.L., Knisely, J.P., Wang, S.L., Yu, J.B., Kupersmith, M.J., 2010. Long-term response to fractionated radiotherapy of presumed optic nerve sheath meningioma. Br. J. Ophthalmol. 94, 559–563.
Levy, R.L., Miller, N.R., 2006. Hyperbaric oxygen therapy for radiation-induced optic neuropathy. Ann. Acad. Med. Singapore 35, 151–157.
Li, Z., Liu, W., Kang, Z., Lv, S., Han, C., Yun, L., Sun, X., Zhang, J.H., 2008. Mechanism of hyperbaric oxygen preconditioning in neonatal hypoxia–ischemia rat model. Brain Res. 1196, 151–156.
Li, F., Fang, L., Huang, S., Yang, Z., Nandi, J., Thomas, S., Chen, C., Camporesi, E., 2011. Hyperbaric oxygenation therapy alleviates chronic constrictive injury-induced neuropathic pain and reduces tumor necrosis factor-alpha production. Anesth. Analg. 113, 626–633.
Lim, Y.B., Pyun, B.J., Lee, H.J., Jeon, S.R., Jin, Y.B., Lee, Y.S., 2011. Proteomic identification of radiation response markers in mouse intestine and brain. Proteomics 11, 1254–1263.
Lin, S., Shyu, K.G., Lee, C.C., Wang, B.W., Chang, C.C., Liu, Y.C., Huang, F.Y., Chang, H., 2002. Hyperbaric oxygen selectively induces angiopoietin-2 in human umbilical vein endothelial cells. Biochem. Biophys. Res. Commun. 296, 710–715.
Linard, C., Marquette, C., Mathieu, J., Pennequin, A., Clarencon, D., Mathe, D., 2004. Acute induction of inflammatory cytokine expression after gamma-irradiation in the rat: effect of an NF-kappaB inhibitor. Int. J. Radiat. Oncol. Biol. Phys. 58, 427–434.
Lindgren, T., Stigbrand, T., Riklund, K., Johansson, L., Eriksson, D., in press. Gene expression profiling in MOLT-4 cells during gamma-radiation-induced apoptosis. Tumour Biol. : J Int. Soc. Oncodev. Biol. Med.
Liu, J.L., Tian, D.S., Li, Z.W., Qu, W.S., Zhan, Y., Xie, M.J., Yu, Z.Y., Wang, W., Wu, G., 2010. Tamoxifen alleviates irradiation-induced brain injury by attenuating microglial inflammatory response in vitro and in vivo. Brain Res. 1316, 101–111.

Please cite this article as: Kuffler, D.P., Hyperbaric oxygen therapy: Can it prevent irradiation-induced necrosis? Exp. Neurol. (2012), doi:10.1016/j.expneurol.2012.03.011

Mahadevan, A., Floyd, S., Wong, E., Chen, C., Kasper, E., 2011. Clinical outcome after hypofractionated stereotactic radiotherapy (HSRT) for benign skull base tumors. Comput. Aided Surg. 16, 112–120.
Mattern, J., Buchler, M.W., Herr, I., 2007. Cell cycle arrest by glucocorticoids may protect normal tissue and solid tumors from cancer therapy. Cancer Biol. Ther. 6, 1345–1354.
Matuschek, C., Bolke, E., Nawatny, J., Hoffmann, T.K., Peiper, M., Orth, K., Gerber, P.A., Rusnak, E., Lammering, G., Budach, W., 2011. Bevacizumab as a treatment option for radiation-induced cerebral necrosis. Strahlenther. Onkol. 187, 135–139.
McLarnon, J.G., Franciosi, S., Wang, X., Bae, J.H., Choi, H.B., Kim, S.U., 2001. Acute actions of tumor necrosis factor-alpha on intracellular Ca(2+) and K(+) currents in human microglia. Neuroscience 104, 1175–1184.
Mihalcea, O., Arnold, A.C., 2008. Side effect of head and neck radiotherapy: optic neuropathy. Oftalmologia 52, 36–40.
Min, J.K., Cho, Y.L., Choi, J.H., Kim, Y., Kim, J.H., Yu, Y.S., Rho, J., Mochizuki, N., Kim, Y.M., Oh, G.T., Kwon, Y.G., 2007. Receptor activator of nuclear factor (NF)-kappaB ligand (RANKL) increases vascular permeability: impaired permeability and angiogenesis in eNOS-deficient mice. Blood 109, 1495–1502.
Mizoguchi, Y., Monji, A., Kato, T.A., Horikawa, H., Seki, Y., Kasai, M., Kanba, S., Yamada, S., 2011. Possible role of BDNF-induced microglial intracellular Ca(2+) elevation in the pathophysiology of neuropsychiatric disorders. Mini Rev. Med. Chem. 11, 575–581.
Moon, Y.J., Lee, J.Y., Oh, M.S., Pak, Y.K., Park, K.S., Oh, T.H., Yune, T.Y., 2012. Inhibition of inflammation and oxidative stress by *Angelica dahuricae* radix extract decreases apoptotic cell death and improves functional recovery after spinal cord injury. J. Neurosci. Res. 90, 243–256.
Morabito, C., Bosco, G., Pilla, R., Corona, C., Mancinelli, R., Yang, Z., Camporesi, E.M., Fano, G., Mariggio, M.A., 2011. Effect of pre-breathing oxygen at different depth on oxidative status and calcium concentration in lymphocytes of scuba divers. Acta physiol. 202, 69–78.
Moravan, M.J., Olschowka, J.A., Williams, J.P., O'Banion, M.K., 2011. Cranial irradiation leads to acute and persistent neuroinflammation with delayed increases in T-cell infiltration and CD11c expression in C57BL/6 mouse brain. Radiat. Res. 176, 459–473.
Mukherjee, D., Coates, P.J., Lorimore, S.A., Wright, E.G., 2012. The in vivo expression of radiation-induced chromosomal instability has an inflammatory mechanism. Radiat. Res. 177, 18–24.
Murphy, C.A., Hoek, R.M., Wiekowski, M.T., Lira, S.A., Sedgwick, J.D., 2002. Interactions between hemopoietically derived TNF and central nervous system-resident glial chemokines underlie initiation of autoimmune inflammation in the brain. J. Immunol. 169, 7054–7062.
Narozny, W., Sicko, Z., Kot, J., Stankiewicz, C., Przewozny, T., Kuczkowski, J., 2005. Hyperbaric oxygen therapy in the treatment of complications of irradiation in head and neck area. Undersea Hyperb. Med. : J. Undersea Hyperb. Med. Soc. Inc 32, 103–110.
Nazario, J., Kuffler, D.P., 2011. Hyperbaric oxygen therapy and promoting neurological recovery following nerve trauma. Undersea Hyperb. Med. : J. Undersea Hyperb. Med. Soc. Inc 38, 345–366.
Niederberger, E., Schmidtko, A., Rothstein, J.D., Geisslinger, G., Tegeder, I., 2003. Modulation of spinal nociceptive processing through the glutamate transporter GLT-1. Neuroscience 116, 81–87.
Nittby, H., Brun, A., Eberhardt, J., Malmgren, L., Persson, B.R., Salford, L.G., 2009. Increased blood–brain barrier permeability in mammalian brain 7 days after exposure to the radiation from a GSM-900 mobile phone. Pathophysiol. : Off. J Int. Soc. Pathophysiol. / ISP 16, 103–112.
Nordal, R.A., Wong, C.S., 2005. Molecular targets in radiation-induced blood–brain barrier disruption. Int. J. Radiat. Oncol. Biol. Phys. 62, 279–287.
Osato, K., Sato, Y., Ochiishi, T., Osato, A., Zhu, C., Sato, M., Swanpalmer, J., Modjtahedi, N., Kroemer, G., Kuhn, H.G., Blomgren, K., 2010. Apoptosis-inducing factor deficiency decreases the proliferation rate and protects the subventricular zone against ionizing radiation. Cell Death Dis. 1, e84.
Otori, Y., Kusaka, S., Kawasaki, A., Morimura, H., Miki, A., Tano, Y., 2003. Protective effect of nilvadipine against glutamate neurotoxicity in purified retinal ganglion cells. Brain Res. 961, 213–219.
Pena, L.A., Fuks, Z., Kolesnick, R.N., 2000. Radiation-induced apoptosis of endothelial cells in the murine central nervous system: protection by fibroblast growth factor and sphingomyelinase deficiency. Cancer Res. 60, 321–327.
Perez-Espejo, M.A., Garcia-Fernandez, R., Tobarra-Gonzalez, B.M., Palma-Copete, J.D., Gonzalez-Lopez, A., De la Fuente-Munoz, I., Salinas-Ramos, J., Felipe-Murcia, M., Martinez-Lage, J.F., Fernandez-Perez, J., Romero, J.M., 2009. Usefulness of hyperbaric oxygen in the treatment of radionecrosis and symptomatic brain edema after LINAC radiosurgery. Neurocirugia 20, 449–453.
Petsuksiri, J., Sermsree, A., Thephamongkhol, K., Keskool, P., Thongyai, K., Chansilpa, Y., Pattaranutaporn, P., 2011. Sensorineural hearing loss after concurrent chemoradiotherapy in nasopharyngeal cancer patients. Radiat. Oncol. 6, 19.
Pratheeshkumar, P., Raphael, T.J., Kuttan, G., 2010. Protective role of perillic acid against radiation-induced oxidative stress, cytokine profile, DNA damage, and intestinal toxicity in mice. J. Environ. Pathol. Toxicol. Oncol. : Off organ Int. Soc. Environ. Toxicol. Cancer 29, 199–212.
Przybyszewska, M., Miloszewska, J., Rzonca, S., Trembacz, H., Pysniak, K., Kotlarz, A., Swoboda, P., Zalewska, M., Malecki, M., 2011. Soluble TNF-alpha receptor I encoded on plasmid vector and its application in experimental gene therapy of radiation-induced lung fibrosis. Arch. Immunol. Ther. Exp. (Warsz.) 59, 315–326.
Qiu, W., Wei, R., Zhang, C., Leng, W., Wang, W., 2010. A glycine site-specific NMDA receptor antagonist protects retina ganglion cells from ischemic injury by modulating apoptotic cascades. J. Cell. Physiol. 223, 819–826.
Raber, J., Rola, R., LeFevour, A., Morhardt, D., Curley, J., Mizumatsu, S., VandenBerg, S.R., Fike, J.R., 2004. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. Radiat. Res. 162, 39–47.
Ramirez, G., Rey, S., von Bernhardi, R., 2008. Proinflammatory stimuli are needed for induction of microglial cell-mediated AbetaPP_{244-C} and Abeta-neurotoxicity in hippocampal cultures. J. Alzheimer's Dis. : JAD 15, 45–59.
Rieken, S., Habermehl, D., Mohr, A., Wuerth, L., Lindel, K., Weber, K., Debus, J., Combs, S.E., 2011. Targeting alphanubeta3 and alphanubeta5 inhibits photon-induced hypermigration of malignant glioma cells. Radiat. Oncol. 6, 132.
Rinaldi, B., Cuzzocrea, S., Donniacuo, M., Capuano, A., Di Palma, D., Imperatore, F., Mazzon, E., Di Paola, R., Sodano, L., Rossi, F., 2011. Hyperbaric oxygen therapy reduces the toll-like receptor signaling pathway in multiple organ failures. Intensive Care Med. 37, 1110–1119.
Rodriguez-Gonzalez, R., Agulla, J., Perez-Mato, M., Sobrino, T., Castillo, J., 2011. Neuroprotective effect of neuroserpin in rat primary cortical cultures after oxygen and glucose deprivation and tPA. Neurochem. Int. 58, 337–343.
Rola, R., Raber, J., Rizk, A., Otsuka, S., VandenBerg, S.R., Morhardt, D.R., Fike, J.R., 2004. Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice. Exp. Neurol. 188, 316–330.
Rosi, S., Andres-Mach, M., Fishman, K.M., Levy, W., Ferguson, R.A., Fike, J.R., 2008. Cranial irradiation alters the behaviorally induced immediate-early gene arc (activity-regulated cytoskeleton-associated protein). Cancer Res. 68, 9763–9770.
Sabatasso, S., Laissue, J.A., Hlushchuk, R., Graber, W., Bravin, A., Brauer-Krisch, E., Corde, S., Blattmann, H., Gruber, G., Djonov, V., 2011. Microbeam radiation-induced tissue damage depends on the stage of vascular maturation. Int. J. Radiat. Oncol. Biol. Phys. 80, 1522–1532.
Safra, T., Gutman, G., Fishlev, G., Soyfer, V., Gall, N., Lessing, J.B., Almog, R., Matcievsky, D., Grisaru, D., 2008. Improved quality of life with hyperbaric oxygen therapy in patients with persistent pelvic radiation-induced toxicity. Clin. Oncol. (R. Coll. Radiol.) 20, 284–287.
Sakaue, M., Mori, N., Makita, M., Fujishima, K., Hara, S., Arishima, K., Yamamoto, M., 2009. Acceleration of methylmercury-induced cell death of rat cerebellar neurons by brain-derived neurotrophic factor in vitro. Brain Res. 1273, 155–162.
Schilling, T., Eder, C., 2011. Sodium dependence of lysophosphatidylcholine-induced caspase-1 activity and reactive oxygen species generation. Immunobiology 216, 118–125.
Shi, W., Wang, Z., Pu, J., Wang, R., Guo, Z., Liu, C., Sun, J., Gao, L., Zhou, R., 2011. Changes of blood–brain barrier permeability following intracerebral hemorrhage and the therapeutic effect of minocycline in rats. Acta Neurochir. Suppl. 110, 61–67.
Shimojo, M., Takasugi, K., Yamamoto, I., Funato, H., Mochizuki, H., Kohsaka, S., 1999. Neuroprotective action of a novel compound–M50463–in primary cultured neurons. Brain Res. 815, 131–139.
Silei, V., Fabrizi, C., Venturini, G., Salmona, M., Bugiani, O., Tagliavini, F., Lauro, G.M., 1999. Activation of microglial cells by PrP and beta-amyloid fragments raises intracellular calcium through L-type voltage sensitive calcium channels. Brain Res. 818, 168–170.
Sminia, P., van der Kleij, A.J., Carl, U.M., Feldmeier, J.J., Hartmann, K.A., 2003a. Prophylactic hyperbaric oxygen treatment and rat spinal cord re-irradiation. Cancer Lett. 191, 59–65.
Sminia, P., van der Kleij, A.J., Carl, U.M., Feldmeier, J.J., Hartmann, K.A., 2003b. Prophylactic hyperbaric oxygen treatment and rat spinal cord re-irradiation. Cancer Lett. 191, 59–65.
Son, E.W., Cho, C.K., Rhee, D.K., Pyo, S., 2001. Inhibition of gamma-irradiation induced adhesion molecules and NO production by alginate in human endothelial cells. Arch. Pharm. Res. 24, 466–471.
Son, E.W., Rhee, D.K., Pyo, S., 2006. Gamma-irradiation-induced intercellular adhesion molecule-1 (ICAM-1) expression is associated with catalase: activation of Ap-1 and JNK. J. Toxicol. Environ. Health A 69, 2137–2155.
Spiegelberg, L., Djasim, U.M., van Neck, H.W., Wolvius, E.B., van der Wal, K.G., 2010. Hyperbaric oxygen therapy in the management of radiation-induced injury in the head and neck region: a review of the literature. J. Oral Maxillofac. Surg. : Off. J. Am. Assoc. Oral Maxillofac. Surg. 68, 1732–1739.
Stancanello, J., Romanelli, P., Pantelis, E., Sebastiano, F., Modugno, N., 2009. Atlas-based functional radiosurgery: early results. Med. phys. 36, 457–463.
Sumen, G., Cimsit, M., Eroglu, L., 2001. Hyperbaric oxygen treatment reduces carrageenan-induced acute inflammation in rats. Eur. J. Pharmacol. 431, 265–268.
Sun, L., Zhou, W., Mueller, C., Sommer, C., Heiland, S., Bauer, A.T., Marti, H.H., Veltkamp, R., 2010. Oxygen therapy reduces secondary hemorrhage after thrombolysis in thromboembolic cerebral ischemia. J. Cereb. Blood Flow Metab. : Off. J. Int. Soc. Cereb. Blood Flow Metab. 30, 1651–1660.
Teguh, D.N., Levendag, P.C., Noever, I., Voet, P., van der Est, H., van Rooij, P., Dumans, A.G., de Boer, M.F., van der Huls, M.P., Sterk, W., Schmitz, P.I., 2009a. Early hyperbaric oxygen therapy for reducing radiotherapy side effects: early results of a randomized trial in oropharyngeal and nasopharyngeal cancer. Int. J. Radiat. Oncol. Biol. Phys. 75, 711–716.
Teguh, D.N., Levendag, P.C., Noever, I., Voet, P., van der Est, H., van Rooij, P., Dumans, A.G., de Boer, M.F., van der Huls, M.P., Sterk, W., Schmitz, P.I., 2009b. Early hyperbaric oxygen therapy for reducing radiotherapy side effects: early results of a randomized trial in oropharyngeal and nasopharyngeal cancer. Int. J. Radiat. Oncol. Biol. Phys. 75, 711–716.
Temel, S.G., Kahveci, Z., 2009. Cyclooxygenase-2 expression in astrocytes and microglia in human oligodendroglioma and astrocytoma. J. Mol. Histol. 40, 369–377.
Terzoudi, G.I., Hatzi, V.I., Donta-Bakoyianni, C., Pantelias, G.E., 2011. Chromatin dynamics during cell cycle mediate conversion of DNA damage into chromatid breaks and affect formation of chromosomal aberrations: biological and clinical significance. Mutat. Res. 711, 174–186.
Toescu, E.C., Moller, T., Kettenmann, H., Verkhratsky, A., 1998. Long-term activation of capacitative Ca2+ entry in mouse microglial cells. Neuroscience 86, 925–935.
Torcuator, R., Zuniga, R., Mohan, Y.S., Rock, J., Doyle, T., Anderson, J., Gutierrez, J., Ryu, S., Jain, R., Rosenblum, M., Mikkelsen, T., 2009. Initial experience with bevacizumab treatment for biopsy confirmed cerebral radiation necrosis. J. Neurooncol 94, 63–68.

Please cite this article as: Kuffler, D.P., Hyperbaric oxygen therapy: Can it prevent irradiation-induced necrosis? Exp. Neurol. (2012), doi:10.1016/j.expneurol.2012.03.011

Tuan, J.K., Ha, T.C., Ong, W.S., Siow, T.R., Tham, I.W., Yap, S.P., Tan, T.W., Chua, E.T., Fong, K.W., Wee, J.T., in press. Late toxicities after conventional radiation therapy alone for nasopharyngeal carcinoma. Radiother. Oncol. : J. Eur. Soc. Ther. Radiol. Oncol.

Tumerdem-Ulug, B., Kuran, I., Ozden, B.C., Mete, O., Kemikler, G., Aktas, S., Calik, B., 2011. Does hyperbaric oxygen administration before or after irradiation decrease side effects of irradiation on implant sites? Ann. Plast. Surg. 67, 62–67.

Velickovic, N., Djordjevic, A., Drakulic, D., Stanojevic, I., Secerov, B., Horvat, A., 2009. Cranial irradiation modulates hypothalamic–pituitary–adrenal axis activity and corticosteroid receptor expression in the hippocampus of juvenile rat. Gen. Physiol. Biophys. 28, 219–227 Spec No.

Veltkamp, R., Siebing, D.A., Sun, L., Heiland, S., Bieber, K., Marti, H.H., Nagel, S., Schwab, S., Schwaninger, M., 2005. Hyperbaric oxygen reduces blood–brain barrier damage and edema after transient focal cerebral ischemia. Stroke; J. Cereb. Circ. 36, 1679–1683.

Vernimmen, F.J., Mohamed, Z., Slabbert, J.P., Wilson, J., 2009. Long-term results of stereotactic proton beam radiotherapy for acoustic neuromas. Radiother. Oncol. : J. Eur. Soc. Ther. Radiol. Oncol. 90, 208–212.

Vlodavsky, E., Palzur, E., Soustiel, J.F., 2006. Hyperbaric oxygen therapy reduces neuroinflammation and expression of matrix metalloproteinase-9 in the rat model of traumatic brain injury. Neuropathol. Appl. Neurobiol. 32, 40–50.

Vollmann, H., Wolfel, S., Ohneseit, P., Stransky, E., Vonthein, R., Wick, W., Meyermann, R., Simon, P., 2007. Differential expression of egr1 and activation of microglia following irradiation in the rat brain. Strahlenther. Onkol. 183, 248–255.

Wanebo, J.E., Kidd, G.A., King, M.C., Chung, T.S., 2009. Hyperbaric oxygen therapy for treatment of adverse radiation effects after stereotactic radiosurgery of arteriovenous malformations: case report and review of literature. Surg. Neurol. 72, 162–167 discussion 167–168..

Wang, X., Chen, S., Ma, G., Ye, M., Lu, G., 2005. Involvement of proinflammatory factors, apoptosis, caspase-3 activation and Ca2+ disturbance in microglia activation-mediated dopaminergic cell degeneration. Mech. Ageing Dev. 126, 1241–1254.

Wang, M.Q., Zou, Q., He, Q., Guan, Y.S., 2009. Gamma knife-treated hepatoma: case of obstructive jaundice and management. Integr. Cancer Ther. 8, 280–282.

Wang, B.W., Lin, C.M., Wu, G.J., Shyu, K.G., 2011. Tumor necrosis factor-alpha enhances hyperbaric oxygen-induced visfatin expression via JNK pathway in human coronary arterial endothelial cells. J. Biomed. Sci. 18, 27.

Wasilewska, J., Sienkiewicz-Szlapka, E., Kuzbida, E., Jarmolowska, B., Kaczmarski, M., Kostyra, E., 2011. The exogenous opioid peptides and DPPIV serum activity in infants with apnoea expressed as apparent life threatening events (ALTE). Neuropeptides 45, 189–195.

Westergaard, E., 1978. The effect of serotonin on the blood–brain barrier to proteins. J. Neural Transm. Suppl. 9–15.

Williamson, R.A., 2007. An experimental study of the use of hyperbaric oxygen to reduce the side effects of radiation treatment for malignant disease. Int. J. Oral Maxillofac. Surg. 36, 533–540.

Wilson, C.M., Gaber, M.W., Sabek, O.M., Zawaski, J.A., Merchant, T.E., 2009. Radiation-induced astrogliosis and blood–brain barrier damage can be abrogated using anti-TNF treatment. Int. J. Radiat. Oncol. Biol. Phys. 74, 934–941.

Winocur, G., Wojtowicz, J.M., Sekeres, M., Snyder, J.S., Wang, S., 2006. Inhibition of neurogenesis interferes with hippocampus-dependent memory function. Hippocampus 16, 296–304.

Wu, C.T., Chen, W.C., Lin, P.Y., Liao, S.K., Chen, M.F., 2009. Androgen deprivation modulates the inflammatory response induced by irradiation. BMC Cancer 9, 92.

Xiao, X., Shi, D., Liu, L., Wang, J., Xie, X., Kang, T., Deng, W., 2011. Quercetin suppresses cyclooxygenase-2 expression and angiogenesis through inactivation of P300 signaling. PLoS One 6, e22934.

Yamashita, T., Shoge, M., Oda, E., Yamamoto, Y., Giddings, J.C., Kashiwagi, S., Suematsu, M., Yamamoto, J., 2006. The free-radical scavenger, edaravone, augments NO release from vascular cells and platelets after laser-induced, acute endothelial injury in vivo. Platelets 17, 201–206.

Yen, C.P., Khaled, M.A., Schwyzer, L., Vorsic, M., Dumont, A.S., Steiner, L., 2010. Early draining vein occlusion after gamma knife surgery for arteriovenous malformations. Neurosurgery 67, 1293–1302 discussion 1302..

Yeung, A.H., Sughrue, M.E., Kane, A.J., Tihan, T., Cheung, S.W., Parsa, A.T., 2009. Radiobiology of vestibular schwannomas: mechanisms of radioresistance and potential targets for therapeutic sensitization. Neurosurg. Focus 27, E2.

Yin, E., Nelson, D.O., Coleman, M.A., Peterson, L.E., Wyrobek, A.J., 2003. Gene expression changes in mouse brain after exposure to low-dose ionizing radiation. Int. J. Radiat. Biol. 79, 759–775.

Yoshida, H., Yanai, H., Namiki, Y., Fukatsu-Sasaki, K., Furutani, N., Tada, N., 2006. Neuroprotective effects of edaravone: a novel free radical scavenger in cerebrovascular injury. CNS Drug Rev. 12, 9–20.

Yu, Y., Matsuyama, Y., Yanase, M., Ito, S., Adachi, K., Satake, K., Ishiguro, N., Kiuchi, K., 2004. Effects of hyperbaric oxygen on GDNF expression and apoptosis in spinal cord injury. Neuroreport 15, 2369–2373.

Zakrzewska, J.M., Akram, H., 2011. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. Cochrane Database Syst. Rev. 9, CD007312.

Zawaski, J.A., Gaber, M.W., Sabek, O.M., Wilson, C.M., Duntsch, C.D., Merchant, T.E., in press. Effects of irradiation on brain vasculature using an in situ tumor model. Int. J. Radiat. Oncol. Biol. Phys.

Zhang, D.K., He, F.Q., Li, T.K., Pang, X.H., Cui de, J., Xie, Q., Huang, X.L., Gan, H.T., 2010. Glial-derived neurotrophic factor regulates intestinal epithelial barrier function and inflammation and is therapeutic for murine colitis. J. Pathol. 222, 213–222.

Zhang, Z.J., Cheang, L.C., Wang, M.W., Lee, S.M., 2011. Quercetin exerts a neuroprotective effect through inhibition of the iNOS/NO system and pro-inflammation gene expression in PC12 cells and in zebrafish. Int. J. Mol. Med. 27, 195–203.

Zhu, C., Huang, Z., Gao, J., Zhang, Y., Wang, X., Karlsson, N., Li, Q., Lannering, B., Bjork-Eriksson, T., Georg Kuhn, H., Blomgren, K., 2009. Irradiation to the immature brain attenuates neurogenesis and exacerbates subsequent hypoxic–ischemic brain injury in the adult. J. Neurochem. 111, 1447–1456.

Zou, J.Y., Crews, F.T., 2005. TNF alpha potentiates glutamate neurotoxicity by inhibiting glutamate uptake in organotypic brain slice cultures: neuroprotection by NF kappa B inhibition. Brain Res. 1034, 11–24.

Please cite this article as: Kuffler, D.P., Hyperbaric oxygen therapy: Can it prevent irradiation-induced necrosis? Exp. Neurol. (2012), doi:10.1016/j.expneurol.2012.03.011